HYPERVALENT COMPOUNDS OF SULFUR, IODINE, AND OXYGEN BEARING FLUORINATED SUBSTITUENTS

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
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By

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Major Department: Chemistry

Reactions of difluorocarbene generated from trimethylsilyl fluorosulfanyl difluoroacetate with cyclic ethers give unique products which can be explained by the formation of the oxonium ylide intermediate followed by a nucleophilic attack to give a ring-opened ether product bearing a difluoromethyl substituent on the oxygen. Other investigations were undertaken to elucidate the poor reactivity of the enolates of esters bearing the hypervalent pentafluorosulfanyl moiety with electrophiles. Under exchange conditions with perdeuterated methanol and a catalytic amount of methoxide ion, the incorporation deuterium confirms the formation of the enolate. Given this result, electronic and steric arguments are invoked to explain the lack of reactivity of the enolates. Other work was undertaken to compare the reactivity of SF_5Br with SF_5Cl as well as general preparative methods for incorporating SF_5 into organic compounds. Maintaining the theme of hypervalency, some initial work is described for the formation of phenyl (trifluoromethylphenyl) iodonium salts. Subsequent palladium-catalyzed cross

coupling reactions with benzene thiol and terminal alkynes provide products containing a trifluoromethylphenyl substituent. This work suggests that the more electron-rich substituent behaves as the nucleofuge.

CHAPTER 1
INTRODUCTION TO THE CHEMISTRY OF THE PENTAFLUOROSULFANYL MOIETY

1.1 Introduction

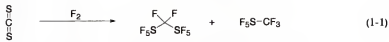
Over the last two decades there has been a significant increase in published reports pertaining to fluorinated compounds. This interest has been, in no small part, due to the unique properties that fluorine exerts on organic compounds. Fluorine induces dramatic effects in molecules due to the small size and high electronegativity. As such, fluorinated molecules have found a host of applications as electronic materials, polymers (e.g., Teflon®), blood substitutes, and physiologically active compounds. More recently, however, an interest in the selective fluorination of molecules has become more prevalent in the literature. Selective fluorination is particularly applicable to the synthesis of the physiologically active molecules and use in medicinal chemistry for the imaging of tumors using positron emission spectroscopy (PET). The use of the trifluoromethyl group to influence the electronic and steric features of a molecule have been well demonstrated in recent years. The pentafluorosulfanyl (SF_5) is another functional perfluorinated group that mimics the electronic and steric factors of the trifluoromethyl group. Although the chemistry associated with the synthesis and incorporation of the pentafluorosulfanyl group was introduced by Case and coworkers in the 1960's,[1] only in recent years has the chemistry of the pentafluorosulfanyl group been revived.

1.2 Preparation of SF_5 Organic Compounds

The number of methods for the direct synthesis of the SF_5 group is limited due to the difficulty of introducing fluorine selectively into the molecule. A number of fluorinating reagents exist for the synthesis of the pentafluorosulfanyl group, but many of these fluorinating reagents are nonselective and lead to the incorporation of fluorine throughout the molecule. Herein, some of the more favorable and historically important methods for the formation of the pentafluorosulfanyl group will be discussed. However, most of the chemistry discussed from the historical perspective will focus on the formation of the pentafluorosulfanyl halides, as these compounds are very important for the methods used to incorporate SF_5 into compounds today.

1.2.1 Direct Fluorination of Thiols

Quite clearly all of the methods required to form the SF_5 group must rely upon a fluorinating reagent. The simplest and most direct reagent is obviously diatomic fluorine gas. By this way, a number of compounds containing SF_5 were prepared from the thiols. Tyczkowski and Bigelow[2] reported on the gas phase fluorination of carbon disulfide using a glass reactor system under mild fluorinating conditions to give the products trifluoromethylpentafluorosulfide and the difluoromethyl(bis)pentafluorosulfide (eq 1-1) among other products in the nonselective fluorination process. The synthesis of trifluoromethyl sulfur pentafluoride was first achieved by oxidizing methyl mercaptan with cobalt trifluoride[3] and also by reaction with fluorine gas.[1] However, it was discovered that direct fluorination of carbon disulfide gave better yields of the trifluoromethyl pentafluorosulfide.



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1.2.2 Reaction of Thiols and Disulfides with Metal Fluorides

A number of methods for oxidative fluorination of a molecule are based upon the reaction of a suitable substrate with an appropriate metal fluoride. Typically, fluorination is achieved by passing the substrate over the metal fluoride under gas phase conditions. In this manner, the artificial blood substitute perfluoroadamantane has been prepared from the parent hydrocarbon.[4] A similar method with argentous fluoride has been used to perfluorinate aromatic disulfides to provide the synthetically challenging aromatic sulfur pentafluorides.

1.2.3 Incorporation of SF_5 via Disulfur Decafluoride or SF_5 Halides

The most common methods for the synthesis of carbon-SF_5 bonds rely upon the use of the dimer of SF_5 (disulfur decafluoride) or the pentafluorosulfanyl chloride or bromide. The use of disulfur decafluoride is not regarded as the most practical method since the synthesis of disulfur decafluoride relies upon the SF_5 halide as a synthon. The reaction of SF_5Cl with an alkene to yield the 1,2-adduct across the double bond is a relatively old reaction that dates to 1961 when the thermal reaction was first studied by Case, Ray, and Roberts.[1] Detailed studies of the reaction mechanism for the addition of SF_5X, where X is SF_5, Cl, or Br, and alkenes have shown that the reaction proceeds through radical intermediates with the resulting product reflecting the more stable radical intermediate formed. Homolysis of the SF_5X bond has been carried out under a variety of reaction conditions. Historically, these conditions involve high pressure, high temperature autoclave reactions. Many of these reactions also require long reaction times on the order of weeks to go to completion. As an example, Gard and Winter reacted α-

chloromethylacrylate with SF_5Br at room temperature for three weeks to obtain 68 percent of the SF_5Br adduct; even more sluggish was the reaction of ethyl β-bromoacrylate with it being necessary to heat the reaction mixture to 80-90 degrees Celsius for an extended period of time (ca. 3 weeks).[5]

The reactivity of SF_5Br and SF_5Cl varies significantly. In fact, many reactions that occur with SF_5Cl do not occur with SF_5Br. Likewise, in many instances, substrates with low reactivity usually require SF_5Br. The electrophilicity of the SF_5 radical is reflected in the reactivity with alkenes. As an example, Winter and Gard discovered that the thermal reaction of vinyl acetate with SF_5Br took considerable effort and only meager yields were obtained. Reaction with ethyl acrylate, however, proceeded more readily due to the lowered reactivity of the double bond giving better yields of the desired product. Conversely, Ait-Mohand and Dolbier found the reaction of vinyl acetate with SF_5Cl in the solution phase at -30 °C proceeded to give nearly quantitative yields but no reaction was observed for α, β-unsaturated compounds such as ethyl acrylate.[6] The absence of reaction with acrylates is presumed to arise, in part, from slow chain transfer in the radical reaction with the electrophilic SF_5 radical.

1.3 Synthesis of Pentafluorosulfanyl Halides and Disulfur Decafluoride

All practical syntheses of SF_5 containing compounds require the use of SF_5Cl or SF_5Br. Even the use of S_2F_{10} for the synthesis of organic SF_5 compounds ultimately requires use of a pentafluorosulfanyl halide since S_2F_{10} is produced from reacting the halide with itself. Currently, only SF_5Cl is commercially available. Nevertheless, the synthesis and purification of the chloride seem to be sufficiently difficult so as to keep the commercially available quantities severely low.

The preparation of sulfur chloropentafluoride has been accomplished by several means including the electrolysis of sulfur dichloride and hydrogen fluoride solutions[7] and the analogous gas phase reaction with fluorine.[8] However, those synthetic methods are shortcoming with regard to low yields. The only methods for the production of SF_5Cl or SF_5Br that provide suitable yields rely upon the reduction of SF_4 by the action of a suitable fluoride. Tullock and coworkers reported the synthesis of SF_5Cl using cesium fluoride to reduce sulfur tetrafluoride to the pentafluorosulfur cesium salt followed by reaction with chlorine gas.[9] The reaction was carried out in an autoclave as is typical for metal fluoride mediated syntheses of SF_5Cl and SF_5Br. An earlier reported method developed by Nyman and Roberts described a flow tube reactor design for the synthesis of SF_5Cl by treatment of elemental sulfur with chlorine trifluoride gas.[10] The low yield (30 %) of the pentafluorosulfur obtained in this way and the formation of the significant byproduct and intermediate sulfur tetrafluoride eventually led Nyman and Roberts to improve upon the gas phase synthesis of SF_5Cl by reacting chlorine monofluoride with SF_4 at 350 °C. The yield of SF_5Cl obtained by this method was 85% and was easily removed from residual starting materials and higher order oxidative products.

Other useful methods based upon the reduction of sulfur tetrafluoride for the synthesis of pentafluorosulfur chloride that give good yields of the product have been reported. Schack and coworkers reported on the catalytic cesium fluoride mediated reaction of chlorine monofluoride with the sulfur tetrafluoride[11] and the Seppelt group[12] improved upon Muetterties group's method[9] involving the oxidation of the SF_5 salt with chlorine gas. George and Cotton gave a report on the reaction of disulfur decafluoride with chlorine gas in a radical process at 350 °C in a flow tube reactor system.[13]

Similar methods as those mentioned above exist for the synthesis of SF_5Br employing BrF or BrF_3 as the oxidizing agent.[14,15] Low yields of the pentafluorosulfanyl bromide were obtained by a lengthy reaction of sulfur tetrafluoride with molecular bromine and bromine pentafluoride.[16] Procedures for the formation of SF_5Br and SF_5Cl have been developed based upon the reaction of disulfur decafluoride with molecular bromine or chlorine,[17,18,13] but these methods are redundant because disulfur decafluoride is produced most conveniently from bromide or chloride.[19]

The synthesis of disulfur decafluoride is of less importance than the formation of the pentafluorosulfanyl chloride or bromide due to the low or complete absence of reactivity of disulfur decafluoride with olefins. The poor reactivity of the disulfur decafluoride may be explained in terms of its ability to participate in the radical chain propagations with olefinic compounds. Roberts observed reactions of S_2F_{10} with ethylene, propene, and vinyl chloride. Only in the latter case was a small amount of product corresponding to the addition of S_2F_{10} observed; of the former reactions only propene gave an unisolable compound.[20]

1.4 Electronical and Physical Aspects of the Pentafluorosulfanyl Moiety

The hypervalency of the sulfur atom arising from bonding with the strongly electronegative fluorine atoms gives rise to unique properties that make the pentafluorosulfur moiety a useful group in organic synthesis.

Both SF_5Cl and SF_5Br are toxic gases near room temperature with boiling points of -21 and 31 °C respectively and have an irritating odor similar to hydrogen chloride. SF_5Cl in relative contrast to SF_5Br is fairly stable—decomposition occurs around 400 versus 150 °C—and is not readily decomposed except at high temperature or by the action of basic aqueous solutions.[21]

The arrangement of the bonding atoms around the central sulfur atom is a distorted octahedron. Bond lengths of both the axial and equatorial sulfur-fluorine bonds are similar to each other and are close to 1.57 Å as determined by electron diffraction, X-ray structures and microwave techniques.[22-25] The bond angle for the F_{ax}-S-F_{eq} bond in pentafluorosulfanyl perfluoromethane determined with the electron diffraction and microwave spectroscopy is 89.5 degrees—close to the theoretical 90 degree bond angle associated with octahedral symmetry.[25] The F_{ax}-S-F_{eq} bond angle is only altered by a few degrees by the presence of sterically demanding groups.

The size of the pentafluorosulfanyl group is similar to that of the *tert*-butyl group. The lack of addition of SF_5X to highly hindered olefins has been associated with the steric influence of the SF_5 group when other factors such as electronics are absent. Rotational hindrance in different functional groups attached to the carbon alpha to the sulfur pentafluoride moiety has been observed.[26]

The arrangement of the fluorine ligands around the sulfur atom are reflected in the ^{19}F NMR spectra. The magnetic resonance spectra for organic compounds containing the SF_5 group show a characteristic AB_4 derived from the nonequivalence of the four equatorial fluorines and the single apical fluorine. These resonances typically appear between 100 and 50 ppm with the axial fluorine resonance usually shifted upfield from the equatorial fluorine signal. The hyperfine interaction of the organic moiety with axial fluorine seems to be the only other coupling observed in the fluorine NMR for many or most cases. However, the interaction of the four equatorial fluorines with the protons on the carbon ligand is observed in the ^1H NMR spectra giving a pentet in the absence of other hyperfine interactions.

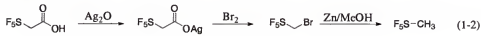
Electronically, the SF_5 is similar to the trifluoromethyl moiety in its ability to stabilize a negative charge. Sheppard conducted a thorough study of the ionizing ability of the SF_5 group in the meta- and para-substituted phenylsulfur pentafluorides by a number of methods including polarographic methods and UV spectrometry.[27] Using these methods, the electron withdrawing ability of the pentafluorosulfanyl moiety was determined to be between the trifluoromethyl group (σ_p=0.53)[28] and the nitro group (σ_p=0.81) with a σ_p value of 0.68. Taft and Sheppard quantitated the inductive effect, σ_I, that the pentafluorosulfanyl group contributes to the σ_p value by the use of ^{19}F NMR to determine the linear free energy relationships[29] and found of 0.53 for σ_I which was in good agreement with the value of 0.55 found by Sheppard using linear free energy relationships derived from the substituted benzoic acids.[27]

The ^{13}C NMR of substituted sultones has been of particular use in the determination of the apparent electronegativity of the pentafluorosulfanyl group. Gard and coworkers calculated the Pauling electronegativity to be 3.62 from the observed effect of the SF_5 group on the chemical shifts. By comparison, the Pauling electronegativity of fluorine is 3.98 and that of chlorine is 3.16.

1.5 Preparation of Pentafluorosulfanyl Compounds

Aside from nonselective fluorination methods of thiols and other sulfur compounds, the only practical method for the incorporation of the SF_5 group is through radical additions of the SF_5Cl, SF_5Br, or S_2F_{10} across double or triple bonds. A suitably functionalized unsaturated compound can then be used to prepare a number of derivatives containing the SF_5 moiety. By this method, alkanes, alkenes, alkynes, aromatic and heteroatomic compounds have been prepared. Regarding the alkanes, pentafluorosulfur

methane is one of the few compounds that cannot be prepared by simple radical addition of the pentafluorosulfanyl halide. One versatile method for the preparation of the SF_5 methane employs the SF_5 acetic acid (**1.1**). Conversion of **1.1** to the silver salt followed by the Hundsdiecker reaction and reduction of the bromide thus obtained provides the SF_5 methane (eq 1-2).



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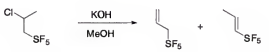
Other alkanes have been prepared by radical addition across the unsaturated bond to provide a variety of alkanes and alkyl halides. The formation of perfluorinated alkyl halides has been reported from the reaction of SF_5Br with the appropriately fluorinated olefin.[2,30]

The preparation of alkenes is convenient in many instances as dehydrohalogenation can be accomplished to form the double bond or the reaction of an alkyne with the pentafluorosulfur halide. The former reaction has been well developed while the latter reaction has been used infrequently. Dehydrohalogenation of the alkane usually results in the formation of the double bond adjacent to the pentafluorosulfanyl group, but exceptions have been reported. Such was the case demonstrated by Case and coworkers who showed that the dehydrohalogenation of the 2-chloropropyl pentafluorosulfanyl gave the vinyl and allyl products, proving that the product formed from the addition of pentafluorosulfanyl chloride was indeed the result of the more stable radical intermediate (eq 1-3).[1]



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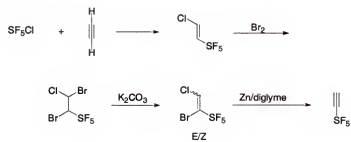
The preparation of fluorinated and deactivated alkenes usually requires the more reactive pentafluorosulfur bromide as the fluorination increases the electrophilicity of the alkene.[31-34] Reactions of SF_5Br with deactivated alkenes are typically accomplished at room temperature; however, fluorinated alkanes can be prepared using SF_5Cl at significantly higher temperatures in the presence of an initiator. As an example, Berry and DeMarco prepared 2-chloro-1-(pentafluorosulfanyl)-2,2-difluoroethane by reacting SF_5Cl with the 1,1-difluoroethylene at 120° in the presence azobis-(2-methylpropionitrile) initiator.[35] It should be noted that most of the alkenes reported in the literature are primary alkenes as sterics influence appears to hinder addition of the SF_5 group to that carbon. There are exceptions as 1,1-bis-(pentafluorosulfanyl)ethane was synthesized by reacting pentafluorosulfanyl ethane with SF_5Cl.

The synthesis of pentafluorosulfur derivatives of alkynes can be prepared by the dehydrohalogenation of alkenes. Hoover and Coffman synthesized ethynylsulfur pentafluoride in poor yields by the lengthy route shown in Scheme 1-1.[36] An alternative and improved method for the synthesis of the acetylene was reported by Gard's research group in which ethyne was reacted with SF_5Br followed by a dehydrobromination.[37] Evidently, attempted formation of the acetylene from the elimination of HCl on the corresponding chloroethylene failed.



Scheme 1-1. Synthesis of pentafluorosulfanyl acetylene.

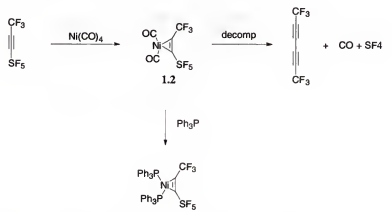
A number of other alkynes have been prepared most notably bis-(pentafluorosulfanyl)ethyne, pentafluorosulfanyl trifluoromethylpropyne[38] and the mono- and bis(pentafluorosulfanyl)diacetylene.[39] Metal salts of terminal alkynes have been prepared by deprotonation with suitable bases.

1.5.2 Preparation of Aryl Pentafluorosulfanyl Derivatives

A number of insecticides and physiologically active compounds containing the pentafluorosulfanyl group on an aromatic group have been detailed in patent literature.[40,41] Thus, a facile method for the incorporation of the SF_5 group becomes necessary. The first detailed preparation of the pentafluorosulfanylbenzene was given by Sheppard who oxidized the diaryl disulfide to trifluorosulfur benzene with argentous fluoride.[42] The trifluorosulfur benzene is essentially an intermediate oxidation product, and treatment of the trifluorosulfur benzene with silver (II) fluoride provided the product in 10% yield. The low yield from this reaction was improved, albeit slightly, by the substituent effect provided by a nitro group in the meta- or para- positions.[43] As an added benefit, the ease of chemical transformation of the nitro group provided a means to a number of aryl derivatives.

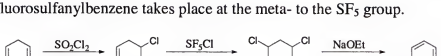
Few other methods exist in the literature for the preparation of aryl pentafluorosulfides. A Diels-Alder reaction was used to synthesize the dimethyl substituted pentafluorosulfanyl cyclohexa-1,4-diene followed by gas phase dehydrogenation to give 3,4-dimethyl-1-(pentafluorosulfanyl)benzene.[36] Bowden and coworkers have prepared ortho-substituted pentafluorosulfanyl benzenes by direct fluorination of aryl thiols.[44] Substitution on the ring is usually limited due to the nature of the fluorinating reagent and the steric bulk of the SF_5 group. Interestingly the only other preparation of ortho-substituted aryl pentafluorosulfides was given by Seppelt's

group whereby 1,2,4-tris(pentafluorosulfanyl)benzene was prepared through a cobalt mediated cyclization.[45,46] An earlier attempt to capitalize upon Reppe's renowned cyclization of acetylenes by reaction of trifluoromethyl(pentafluorosulfanyl) acetylene with a nickel catalyst failed to give the desired cyclization product but rather the nickel carbacycle **1.2** shown in Scheme 1-2 which decomposed in the absence of excess carbon monoxide to give the diacetylene.[35]



Scheme 1-2. Formation and reaction of nickel SF_5 carbacycle.

Dolbier and coworker have described the most recent procedure for the effective formation of the substituted pentafluorosulfanyl benzenes.[47] Unlike the other existing methods for the syntheses of aryl sulfur pentafluorides which require forcing conditions, the method of Dolbier relies upon the previously reported method for the addition of SF_5Cl to alkenes (eq 1-4).[6] The overall yield for this reaction sequence is 70% over three steps starting from 1,4-cyclohexadiene. Further elaboration of the ring can be carried out, but due to the withdrawing effect of the SF_5 group substitution of the pentafluorosulfanylbenzene takes place at the meta- to the SF_5 group.



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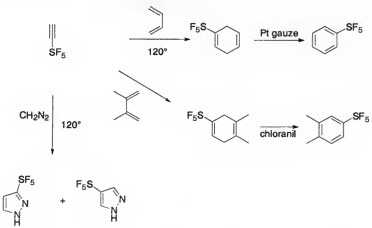
1.5.3 Preparation of Heterocyles and Miscellaneous Pentafluorosulfanyl Compounds

The difficulty of introducing a pentafluorosulfanyl group has not completely prevented the diversification of compounds containing the pentafluorosulfanyl group. A relatively large number of heteroatom containing compounds have been synthesized including ketones, esters, aldehydes, sultones, sulfates, ketenes, aziridines, amines, and oxiranes. In fact, the reactivity of some of these compounds is particularly useful for the preparation of other SF_5 derivatives.



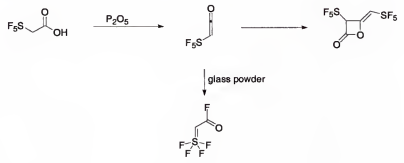
Scheme 1-3. Cycloaddition reactions of pentafluorosulfanyl acetylene.

Early work in the field of SF_5 chemistry by Sheppard included the preparation of pentafluorosulfanyl acetylene which proved useful as a dienophile as well as being able to undergo 1,3-dipolar cycloadditions with diazomethane (Scheme 1-3) to give regioisomeric pyrazoles.[36]

Other cycloadditions reactions have been exploited to give various carbo- and heterocycles. Shreeve and Gard exploited the cycloaddition reaction of sulfur trioxide with (pentafluorosulfanyl)perfluoroethylene to give the four-membered sultone.[48] Perfluorovinylsulfur pentafluoride has proved to be a valuable synthon in a number of other reactions. The formation of a number of cyclic derivatives such as 1,2,2-trifluoro-

1-(pentafluorosulfanyl)-4-vinylcyclobutane,[49] 2,2,3-trifluoro-3-(pentafluorosulfanyl)-4,4-bis(trifluoromethyl)oxetane,[50] and 2,2,3-trifluoro-3-(pentafluorosulfanyl)-N-chlorosulfenyl aziridine[51] are representative examples.

The interesting reactivity of the pentafluorosulfanyl ketene has been exploited in a number of reactions. The ketene can be prepared from pentafluorosulfanyl acetic acid by dehydration with phosphorus pentoxide.[52] Pentafluorosulfanyl ketene is reasonably stable at room temperature but undergoes a presumed intermolecular isomerization in the presence of glass to give the conjugated tetrafluorosulfanylideacetyl fluoride (**1.3**, Scheme 1-4). The β-lactone is obtained by heating the ketene. The expected chemistry associated with the cumulated carbon of SF_5 ketenes upon reaction with nucleophiles takes place.[53,54]



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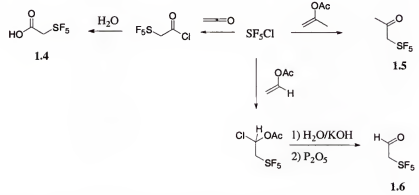
Scheme 1-4. Formation and reactions of pentafluorosulfanyl ketene.

Epoxidation of electrophilic SF_5 compounds such as (pentafluorosulfanyl) perfluoroethylene has been demonstrated by Gard who generated the anionic intermediate by reacting the perfluorovinylsulfur pentafluoride with nucleophilic hypochlorite under phase-transfer conditions. Ring closure results with concomitant elimination of chloride ion.[55]

Organic compounds containing the carbonyl functionality constitute one of the most important classes in organic chemistry. Few other functional groups allow for such ease of transformations at the carbonyl carbon or on the adjacent carbon atom. Hence, the synthesis of ketones, aldehydes, and carboxylic acids constitutes an important area in SF_5 chemistry as the acidity of the α carbon provides a means to introduce substituents thus forming a secondary carbon alpha to the SF_5 group.

Along this vein of chemistry, a number of SF_5 carbonyl compounds have been synthesized, most notably in recent years by Gard. The synthesis of SF_5 acetic acid (**1.4**) can be accomplished by reaction of SF_5Cl with ketene (Scheme 1-5). The acid chloride intermediate thus formed is easily hydrolyzed to provide the acid.[56,57] The hydrolysis of vinyl acetates provides access to the methyl ketone (**1.5**).[57]



Scheme 1-5. Synthesis of pentafluorosulfanyl ethaldehyde

Esterification of the acid is possible under suitable conditions to provide the corresponding esters. Ester derivatives have also been synthesized by solvolysis of acetates, such as shown in Scheme 1-5, followed by oxidation of the acetal intermediate.[58] Similar SF_5 carbonyl compounds have been shown to be viable compounds for carrying out enolate chemistry. Winter and Gard have demonstrated the ability of pentafluorosulfanyl(fluorosulfonyl) acetic acid esters to form a number of

enolates.[59] The enolate salts were, in most examples, sufficiently stable as to be isolated and have a reasonable shelf life of many months.

Many compounds containing the SF_5 group have not been included in the introduction due to the scope of this dissertation. I have, however, tried to include compounds in this introduction that are most notable for the chemistry which they undergo, their uniqueness, or their importance in terms of the difficulty of preparation. The physical properties of the SF_5 group are included due to the unique nature of this moiety in terms of size and electronic properties and the relevance to the research described in the following chapter.

CHAPTER 2
REACTIVITY OF PENTAFLUOROSULFANYL ESTERS AND SYNTHESIS OF ALKANES AND ALKENES BEARING THE PENTAFLUOROSULFANYL SUBSTITUENT

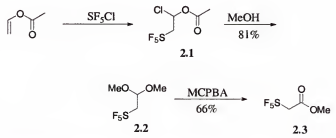
2.1 Investigation of the Enolate Formation of Pentafluorosulfanyl Esters

Our research into the chemistry of pentafluorosulfanyl containing compounds initially began with a new method for the addition of SF_5Cl into organic compounds. Dr. Samia Ait-Mohand discovered that the addition of SF_5Cl to alkenes and even alkynes proceeded readily in a low temperature solution phase reaction when the addition of catalytic triethylborane was added.[6] This method is advantageous in that the classical conditions— long reaction time, high temperature, high pressure autoclave reactions— are avoided. Furthermore, yields with this method are typically very high to excellent. Many reactions proceed to give near quantitative yields. However, the method of Dolbier and Ait-Mohand for the incorporation of SF_5Cl has the primary disadvantage of being limited by the freezing point of the alkene as the reaction requires a homogeneous mixture for good yields. Typically, these reactions are successfully run between -30 and -78° C. Nevertheless, a wide variety of alkenes and alkynes can be successfully reacted in solution phase with SF_5Cl by initiating with triethylborane.

As an extension of the work with SF_5Cl, we were interested in the synthesis of a simple ester containing the SF_5 moiety and the corresponding reactions of the enolate to provide highly substitute carbon atoms bearing the SF_5 group. Furthermore, it was hoped that the formation of the enolate would provide information regarding the electronic

effect of the pentafluorosulfanyl group as the literature, with few exceptions has been remarkably devoid of such information.

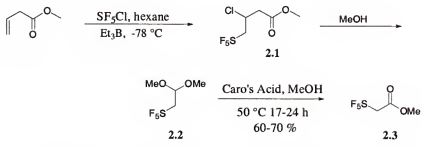
The pentafluorosulfanyl acetic acid methyl ester (**2.3**, Scheme 2-1) had been previously reported in the literature by Gard.[58] His synthesis began with the addition of pentafluorosulfanyl chloride to vinyl acetal in low yield described previously in a patent procedure.[57] Methanolysis of the adduct provided the corresponding methyl acetal, **2.2** in good yield followed by treatment of the clear liquid with meta-chloroperbenzoic acid (MCPBA) at elevated temperature provided the ester.



Scheme 2-1. Gard's synthesis of (pentafluorosulfanyl) acetic acid methyl ester.

Our synthesis of **2.2** closely paralleled Gard's procedure with the initial exception of using our method for the addition of SF_5Cl rather than the patent process described in literature that Gard relied upon. The conversion of the dimethyl acetal to the ester was initially attempted following the preparation in Scheme 2-1. Unfortunately, it was discovered that the literature procedure was difficult to perform on a small scale (ca. 1 gram). Instead of obtaining a homogeneous melt that Gard described, it was observed for the reaction that the meta-chloroperbenzoic acid never completely melted. Subjecting the crude mixture to ^1H NMR did reveal a small pentet in the spectrum for the two methylene protons of the ester but the reaction still contained starting material and was abandoned for an easier approach to the oxidation.

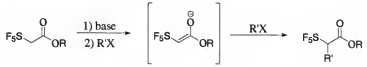
Other oxidizing agents were considered for the conversion of the acetal to the ester. A careful inspection of the literature regarding the oxidation of acetals to the corresponding esters provided a number of methods.[60] The Caro acid (peroxymonosulfuric acid) as an oxidizing agent was chosen to oxidize the acetal to the corresponding acetal as this reagent is liquid at room temperature and, like MCPBA, is a peroxy compound. This reagent proved to be quite suitable as prepared according to the literature[61] for the oxidation of the intermediate SF_5 acetal. Application of gentle heat over 17 hours to the reaction mixture provided the ester cleanly and in slightly better yield than the Gard procedure. Overall our modified synthesis of the ester is shown in Scheme 2-2.



Scheme 2-2. The modified synthesis of (pentafluorosulfanyl) acetic acid methyl ester.

The ester shows a characteristic peak for a carbonyl at 1756 cm^{-1} as well as a strong and broad absorption associated with the S-F stretching modes for the pentafluorosulfanyl group. Multinuclear nuclear magnetic resonance is particularly instructive as well with a pentet corresponding to the methylene protons at 4.30 ppm and a singlet for the methyl group of the ketone near 3.8 ppm. The ^{19}F NMR (Figure 3-1) displays the typical AB_4 spectrum for the SF_5 group with a distorted pentet centered around 78.9 ppm and a doublet of multiplets for the equatorial fluorines at 70.8 ppm. ^{13}C NMR shows a resonance toward the low end of a typical carbonyl carbon at 163 ppm and

a pentet for the methylene carbon at 70.3 ppm. The resonance for the methyl group is typical for an ester at 53.5 ppm.



(2-1)

Table 2-1. Parameters for enolate formation and attempted reaction with electrophiles.

RX	Base	Solvent	Temperature (° C)
MeI	LDA	THF	-78
	^{t}BuOH	dioxane	100
	NaH	dioxane	23
MeI	^{t}BuOK	^{t}BuOH	23
MeI	NaH	DMF	23

With the ester in hand, the attempt to form the enolate and further react it with a variety of electrophiles was made (eq 2-1). Under standard conditions for enolate formation—treating a cold (-78° C) solution of the ketone with lithium diisopropylamide or suitable base—the formation of bright yellow solution followed. The yellow color was perceived as the formation of the lithium enolate of the SF_5 ketone. Other research in the area of anionic SF_5 derivatives has suggested that the formation of colored solutions (typically yellow) correlates to the formation of the anion. Upon formation of the presumed anion, the solution was treated with methyl iodide in anticipation of obtaining the alkylated product. The complete absence of the expected product was extremely surprising considering the electron withdrawing nature of the SF_5 should lower the pK_a for the ester corroborated by the formation of the presumably yellow enolate. The attempt to alkylate the ester was attempted under a variety of conditions as summarized

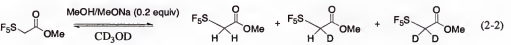
in Table 2-1. Disappointingly this reaction failed in all cases even with the best electrophiles such as allyl bromide. The aldol reaction of benzaldehyde with the enolate in an attempt to form the alcohol or the dehydrated product also failed to give products.

The obvious lack of any reaction gave serious doubt as to whether the enolate anion was even being formed. Furthermore, if the enolate was truly being formed, the question as to why there was no reaction was more troubling. The large steric bulk of the SF_5 group might prevent the attack of the electrophile by the anionic carbon center. ^1H and ^{19}F NMR were used to further study the probable enolate formation in an attempt to answer the pertinent questions with respect to the lack of reactivity. For this study, an NMR sample was prepared using perdeuterated methanol as the lock solvent and a catalytic amount of sodium methoxide in methanol as the base. It was anticipated that methoxide would be a suitable base to generate the enolate anion under exchange conditions ultimately incorporating deuterium at the carbon atom. When a sample of the ester in perdeuterated methanol was treated with a solution containing approximately 10 mole percent of freshly prepared sodium methoxide in methanol, and then subjected to ^1H and ^{19}F NMR, a new signal in addition to that of the ester was observed. The new signal in ^1H NMR is shown Figure 2-2. In the fluorine NMR, a new doublet for the equatorial fluorines appeared upfield from the resonance corresponding to the parent ester and lacks the hyperfine structure that the ester displays. The axial fluorine signal is only slightly perturbed and overlaps with the signal for the ester. Integration of the ^{19}F NMR spectrum for a solution containing 10 mol % of sodium methoxide corroborates the formation of the enolate as the ratio of the new signal as compared to the ester is approximately 1:10 respectively suggesting that the formation of the enolate is quantitative with respect to

base. Inspection of the proton NMR spectrum reveals a pentet of triplets shifted slightly upfield from the methylene protons of the ester.

The appearances of the both the proton and the fluorine NMR spectra are dynamic. Analysis of the sample containing only 0.2 equivalents of methoxide several hours later gives ^{19}F spectrum shown in Figure 2-3. The formation of yet a third species is clearly evident in the fluorine NMR with respect to the high field portion corresponding to the equatorial fluorines. Also, this new signal is devoid of any hyperfine structure. Eventually both the fluorine (Figure 2-4) and the proton NMR reveal the presence of only one major species corresponding to the gem-dideuterio ester. Only the methyl group gives a signal in the proton NMR—the signal for the methylene group is noticeably absent.

Considering that the formation of the new species takes place under exchange conditions and the first species formed clearly indicates the incorporation of deuterium as reflected in the signal for the methylene group, then the most likely the second species corresponds to the structure for the gem-dideuterio ester (**2.5**, eq 2-2).



2.3 **2.4** **2.5**

The reaction given in equation 2-2 supports the NMR results. Upon addition of a catalytic amount of base, ester **2.3** undergoes successive deuterium incorporations. Deuteration at the methylene carbon increases the electron density causing the equatorial fluorine signal to shift upfield. In addition, the loss of hyperfine character can be explained by noting that the gyromagnetic ratio of a deuterium nucleus to that of the hydrogen nucleus is approximately 1 to 6.5 thus leading to a decrease in the linewidth

upon successive deuterations at the methylene carbon. The absence of the enolate ion is presumed to result from exchange broadening of the reaction although no low temperature NMR experiments were conducted to determine the veracity of this assumption.

The results of the NMR experiments are supported by mass spectral analysis of reaction mixtures. The low resolution mass spectrum acquired for the parent ester has a base peak at 169 m/z representing the $SF_5C_2H_2O$ ion. Subjecting the base/ester solution to NMR in perdeuterated methanol followed by quenching the enolate with aqueous hydrochloric acid gives the mixture containing the parent ester and the mono- and dideuterated esters. Inspection of the mass spectrum for this mixture has a parent peak at 169 m/z and smaller peaks of m/z 170 and 171 representing the isotopically substituted material. Furthermore, these peaks are in the same ratio to the parent ester as the peaks in the ^{19}F NMR assigned to monodeuterated and dideuterated esters.

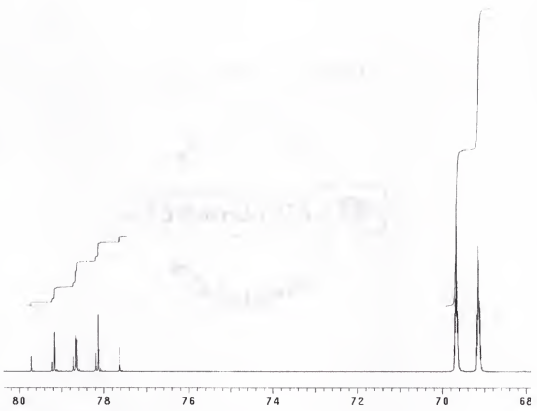


Figure 2-1: ^{19}F NMR of the pentafluorosulfanyl acetic acid methyl ester.

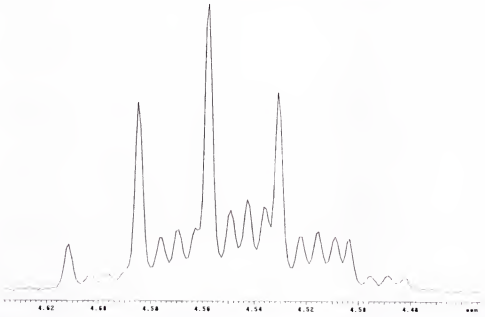


Figure 2-2: The portion of a ^{1}H NMR of the base catalyzed ester solution containing the monodeuterated ester.

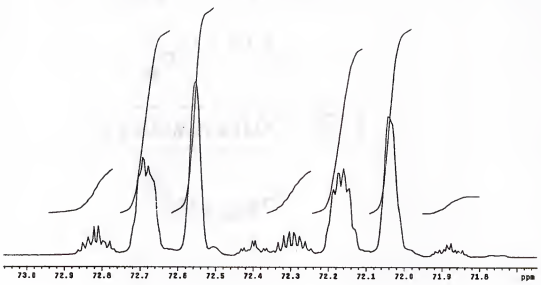


Figure 2-3: ^{19}F NMR of the base catalyzed ester solution containing the three species. Other minor species not identified are visible in this high field portion of the spectrum.

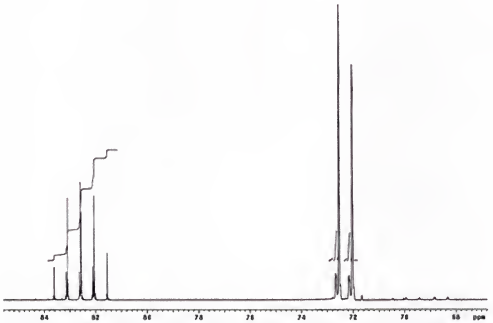
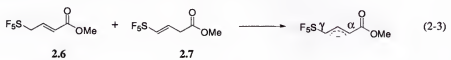


Figure 2-4: The ultimate ^{19}F NMR of the base catalyzed ester solution showing the conversion of the ester to the dideuterio species. A residual peak for the monodeuterated species remains due to protic material from the solvent.

Clearly the results of the NMR experiments coupled with the mass spectral analysis of the quenched reaction mixtures indicate that the formation of the enolate takes place and, the enolate undergoes isotopic substitution under exchange conditions. However, the NMR experiments do not explain the lack of reactivity of the enolate with electrophiles.

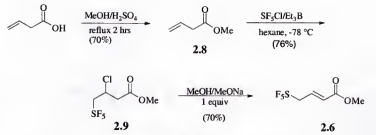
The lack of reactivity of the enolate could be explained by the large steric bulk of the pentafluorosulfanyl group or the stabilization of the anionic center or the culmination of steric and electronic effects. A method was envisioned whereby the steric effect of the pentafluorosulfanyl moiety could further probed by introducing another reactive site. The SF_5 crotonate ester **2.6** (eq 2-3) or allyl ester **2.7** upon deprotonation would become ambident nucleophiles at the α or γ position of the ester.



2.6 **2.7** (2-3)

The synthesis of ester **2.6** was achieved in a straightforward fashion as outlined in Scheme 2-3. The synthesis began with the commercially available vinyl acetic acid which was esterified. The addition of SF_5Cl to the double bond provided an intermediate that could undergo base induced elimination of HCl to provide compound **2.6** or **2.7**. Treatment of the intermediate with base provided the conjugated isomer in 37% yield from the acid.

The formation of the enolate of the (pentafluorosulfanyl)methyl crotonate ester (**2.6**) and subsequent reaction with electrophiles was attempted using the same conditions as for the acetic ester. Once again there was no observed reaction with any electrophiles (Table 2-2).



Scheme 2-3. Synthesis of the (pentafluorosulfanyl)methyl crotonate methyl ester.

Table 2-2. Reaction parameters for crotonate ester

R	Base	Solvent	Temperature (° C)
MeI	LDA	THF	-78
MeI	NaH	Et_2O	-78-23
	MeONa	MeOH	23

NMR studies were again employed to determine the reactivity of the ester in the same method as the first case study with the acetic acid ester. Under the exchange conditions present in a solution of perdeuterated methanol and catalytic methoxide, the formation of deuterated products was realized by observing the disappearance of the starting material. NMR data was corroborated by low resolution mass spectral analysis which displays the isotopically substituted fragments from the products shown in eq 2-4.

The experiments conducted with the acetic and the crotonate ester clearly demonstrate that enolate formation takes place under relatively mild conditions. The

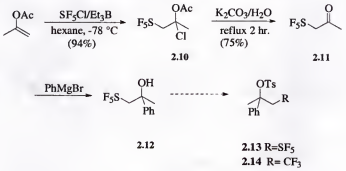
explanation as to why no reaction takes place between what should be a nucleophilic carbon anion and electrophiles must be based on steric or electronic effects or some combination of both.

The results with the acetic ester were helpful with regard to the electronic effects that may be affecting the reactivity of the ester. Further, a straightforward search of the literature revealed that analogous alkylation reactions of the tert-butyl methyl acetate enolate have been reported.[62,63] The ability of the tert-butyl enolate to undergo alkylations coupled with the lack of reactivity displayed by the crotonate system strongly suggest that the electronic properties of the pentafluorosulfanyl group predominately effects the anionic center in such a way as to strongly stabilize the anion alpha to the SF_5 center where steric bulk aids in preventing the reaction with electrophiles.

Other pentafluorosulfanyl ester systems described in the literature were also observed to have little or no reactivity with electrophiles. Gard and coworkers illustrated that the formation and isolation of stable enolate salts was possible.[59] Subsequent reactions of the enolate salts failed to give the expected products. Most likely the failure of pentafluorosulfanyl esters are the result of the stabilization of the anion to give most of the charge density at the carbon alpha to the SF_5 group effectively giving a highly hindered anion such that the approach of electrophiles other than a proton or deuteron is rendered impossible.

The electronic effect of the SF_5 group has received little formal attention in the literature and given the results with the esters, a closer inspection of the electronic effect was attempted. The use of linear free energy relationships has proven to be a useful quantitative method for the determination of substituent effects in the ionization and

solvolysis of suitable substrates. By this method the electron withdrawing effect of the pentafluorosulfanyl group as compared with the trifluoromethyl group was planned via the study of a tertiary pentafluorosulfur methylene phenyl tosylate **2.13** and the corresponding trifluoromethyl substituted compound **2.14** (Scheme 2-4).



Scheme 2-4. Synthetic route to the pentafluorosulfanyl isopropanol.

The attempted synthesis of the pentafluorosulfanyl tosylate (**2.13**) began in straightforward fashion from commercially available isopropenyl acetate. Addition of pentafluorosulfanyl chloride across the double bond took place in excellent yield. The ketone **2.11** was prepared in 75% yield by refluxing the acetate **2.10** in aqueous potassium carbonate to hydrolyze the acetate group with concomitant elimination of chloride ion. The reaction of the ketone readily underwent reaction with phenyl magnesium bromide using standard Grignard conditions to provide the tertiary alcohol (**2.12**).

It was realized early in the synthesis that the most difficult step of the synthesis would be the formation of the tosylate from a tertiary alcohol. The formation of tertiary tosylates is notoriously difficult due to steric hindrance and the propensity for the tosylate to form a carbocation and undergo rearrangements. The synthesis of the SF_5 tosylate (**2.13**) was no different with regard to the steric hindrance. The reaction of the SF_5 alcohol with recrystallized toluenesulfonyl chloride in the presence of pyridine failed to

provide the tosylate. Further attempts were made to form **2.13** or the corresponding methyl sulfonate under more strenuous conditions (heat, strong base) but all efforts failed. Given the structure of the alcohol the failure to transform the alcohol to the tosylate or mesylate was disappointing but easily explained by noting the high degree of steric hindrance.

2.2 Reactions of pentafluorosulfanyl bromide with alkenes and alkynes

The reactivity of pentafluorosulfanyl chloride and the pentafluorosulfanyl bromide with unsaturated compounds, as noted in Chapter 1, is the primary difference between these SF_5 reagents. It was noted during the course of previous research in Dolbier's laboratories that certain reactions between substituted alkenes and the pentafluorosulfanyl chloride failed or resulted in poor yields. Furthermore, the reaction conditions employed to synthesize SF_5 compounds from the pentafluorosulfanyl chloride at low temperature in the solution phase had not previously been attempted using pentafluorosulfanyl bromide. Extending the applicability of this general synthetic method to include pentafluorosulfanyl bromide was important for the synthesis of a wide range of SF_5 containing compounds. Hence, a number of reactions were tried with pentafluorosulfanyl bromide generously provided by Gary Gard from Portland State University.

Despite the slightly higher boiling point of 6° C for the pentafluorosulfanyl bromide, the reactions of SF_5Br with alkenes and alkynes were conducted using the same general procedure as for SF_5Cl. Since the reactivity of the SF_5Br as compared with SF_5Cl was the primary interest, alkenes known to react with SF_5Cl were used as the substrates in the reactions with SF_5Br. It became clear from the result of the first experiment conducted using vinyl acetate, a substrate known to work well with SF_5Cl, that pentafluorosulfanyl bromide behaved quite differently under the given reaction

conditions. In the reaction of vinyl acetate with SF_5Br, the formation of a black deposit on the sides of the flask formed upon initiation of the reaction with triethylborane. Upon removal of the solvent, only a tarry material remained in the flask. In fact, the formation of a black tar was observed in the reaction of other substrates with SF_5Br during the course of this study. Reactions with straight-chain olefins, although not tested extensively due to the limited quantity of SF_5Br, for the most part gave the expected adducts albeit in varying yields (Table 2-3).

Table 2-3. Reactions of SF_5Br and SF_5Cl with various alkenes and alkynes.

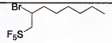
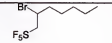
Alkene (alkyne)	% Yield	% Yield (SF_5Cl)	Product
	99	95	 **2.15**
	73	96	 **2.16**
	99	93	 **2.17**
	89	--	 **2.18**
	30-54	98	 **2.20**

Table 2-3 (continued)

 **2.21**	67		 **2.22**
	--	98	NR
	79	49 + 27 (2:1 adduct)	 **2.23**
	--	--	NR
	--	--	NR
	--	--	NR
	--	--	NR
	--	--	NR

As exemplified by Table 2-3, the reaction of pentafluorosulfanyl bromide with alkenes and clearly reveals the lack of reactivity of SF_5Br toward internal alkenes with the exception of cyclohexene. Furthermore, in spite of the increased reactivity reported in literature, the reaction with pentafluoropropene and electrophilic alkenes failed to give the expected adducts. Reactions of the SF_5Br with alkynes proceeded in excellent yield

and gave strictly the trans monomer adduct rather than the 2:1 adduct observed for the reaction of phenylacetylene with SF_5Cl.[6] The structures for the expected products from the reactions of alkynes are presumed to be trans in accord with the steric bulk imposed by the SF_5 group.

The failure of SF_5Br to react with less reactive alkenes, particularly the perfluorinated alkenes under the low temperature reaction conditions in the condensed phase is troubling as fluorinated alkenes have been shown to form the SF_5Br adduct in the gas phase at room temperature.[31] Presumably, the failure to react is a combination of the low temperature and the lowered reactivity of the propagating radical.

2.3 Conclusions

The synthesis of novel pentafluorosulfanyl compounds was performed using triethylborane to initiate the low temperature reaction of olefins with SF_5Cl. The synthesis of novel esters bearing the pentafluorosulfanyl group was achieved in this manner in the anticipation that these esters would be valuable for the synthesis of compounds bearing a pentafluorosulfanyl group alpha to a secondary carbon. Unfortunately, enolates of these esters failed to provide products deriving from the alkylation at the carbon atom. Experiments conducted using nuclear magnetic resonance and mass spectral analysis clearly demonstrate the formation of the enolate intermediate as proton/deuteron exchange takes place under base catalyzed conditions. From these experiments it is postulated that the electronic effect of the pentafluorosulfanyl group localizes the negative charge on the alpha carbon. Hence, the overwhelming steric bulk of the pentafluorosulfanyl group prevents the approach of electrophiles other than a proton or deuteron. A study to determine the extent of the electronic effect of the SF_5 group through linear free energy relationships to the trifluoromethyl group was

abandoned after it was determined that the steric hindrance of the SF_5 group prevented the formation of the tosylate required for the study.

The reactivity of SF_5Br was compared to SF_5Cl using the method of Dolbier and Ait-Mohand was probed using representative alkenes and alkynes. It appears that under the low temperature reaction conditions that the more electrophilic SF_5Br reacts with terminal straight-chain alkenes and more substituted alkynes in good to excellent yields. With more reactive alkenes such as the vinyl acetate and cyclohexene, the reaction proceeds too rapidly giving an intractable tar. However, reactions with electrophilic and substituted alkenes failed to provide the expected adducts using this method. Hence, initial reactions demonstrate that the SF_5Br is more limited with regard to the reactivity of the alkene or alkyne at low temperature.

2.4 Experimental

General experimental procedures: Commercial reagents were used without further purification unless otherwise noted. All NMR spectra were obtained using a 300 Mhz Varian instrument using $CDCl_3$ as a lock solvent and reference unless explicitly stated otherwise. High resolution mass spectral data was acquired on a Finnigan MAT 95Q hybrid-sector mass spectrometer (ThermoFinnigan, San Jose, CA) by the mass spectral laboratory services at the University of Florida. Electron Ionization (EI) was carried out at 70 eV using a direct insertion probe. Chemical Ionization (CI) was carried out at 150 eV using a direct insertion probe in the presence of methane.

Basic solutions containing methoxide were freshly prepared using freshly distilled anhydrous methanol and sodium metal. Amine bases, such as triethylamine, were distilled from calcium hydride and stored over potassium hydroxide pellets. Sodium methoxide solutions used for the NMR studies and n-butyl lithium used to prepare

lithium diisopropylamide and lithium hexamethyldisilazane solutions for conducting alkylation reactions were titrated prior to use. Glassware was flame- or oven-dried for reactions of SF_5Cl or SF_5Br with alkenes or for reactions of enolates. Ethereal solvents were dried over benzophenone ketyl radical and freshly distilled prior to use.

Vinyl acetic acid methyl ester (2.8): A 50 mL round bottom flask was charged with 3 mL (3.03 g, 35.2 mmol) of the vinyl acetic acid and 20 mL of methanol. A catalytic amount (0.05 mL) of concentrated sulfuric acid was added and the flask was sealed and the solution left to stir overnight. The solution was partitioned with ether and water and the aqueous layer was removed. The ether layer was washed with several portions of water, dried with magnesium sulfate and filtered. Ether was removed by distillation and the ester was purified by distillation (105- 109°C) to provide 2.13 g of colorless liquid representing 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.0-5.85 (m, 1H), 5.21-5.11 (dm, 2H), 3.69 (s, 3H), 3.09 (d, 2H, J=6.9 Hz).

1-chloro-2-(pentafluorosulfanyl)ethyl acetate (2.1): A round bottom three-neck flask was flame-dried and fitted with a total reflux condenser, stir bar, septum, and a gas bubbler tube. The flask was charged with 30 mL of hexane and vinyl acetate (1.3 mL, 14.1 mmol) and was cooled with a dry ice/acetonitrile bath (-42 °C). Sulfur pentafluorochloride (3.0 g, 18.4 mmol) was condensed into the solution via the gas bubbler over a period of a few minutes. The solution was allowed to stir for a few minutes and a catalytic amount of 1.0 molar triethylborane (1.4 mL, 1.4 mol, 0.1 equiv) was added. The solution was stirred for 20 minutes at -42 ° before warming to room temperature. The solution was passed through a short length of silica gel and solvent was removed to give 3.1 g (88 %) of 1-chloro-2-(pentafluorosulfanyl)ethyl acetate.

^{1}H NMR ($CDCl_3$): δ 6.89 (dd, 1H, J=9.6, 2.1 Hz); δ 4.16 (mult, 2H); δ 2.2 (s, 3H). ^{19}F NMR ($CDCl_3$): δ 80.4 (pentet, 1F, J=143.8 Hz); δ 66.1 (d of mult, 4F, J=143.8 Hz). ^{13}C NMR ($CDCl_3$): δ 167.78; 76.98 (pentet, J=5.78 Hz), 73.58 (pentet, J=14.6 Hz), 20.63. HRMS: calculated for $C_4H_7O_2ClSF_5$: 248.977545, found 248.9772 (M+H); 496.9506 (2M+H).

1,1-dimethoxy-2-(pentafluorosulfanyl)ethane (2.2): A solution of 1-chloro-2-(pentafluorosulfanyl)ethyl acetate (3.2 g, 12.9 mmol) and 8 mL of anydrous methanol was stirred while maintaining the temperature at 50 ° C overnight. The solution was treated with 5 mL of water and partitioned with 20 mL of diethyl ether. The layers were separated and the ether layer was washed two times with 10 mL portions of water. The aqueous layers were combined and extracted with 10 mL of ether. The ether layers were then combined and dried with anhydrous magnesium sulfate. The diethyl ether was removed under reduced pressure to provide 2.2 g of the acetal in 79% yield. ^{1}H NMR ($CDCl_3$): δ 4.85 (t, 1H, J=5.1 Hz); δ 3.76 (d pentet, 2H, J=8.7, 5.1 Hz); δ 3.38 (s, 6H). ^{19}F NMR ($CDCl_3$): (AB_4) δ 83.46 (p, 1F, J=151.4 Hz): δ 66.22 (dt, 4F,J=148.3, 6.8 Hz). ^{19}F NMR ($CDCl_3$): 99.9 (p, J=5.05 Hz), 71.8 (p, J=12.6 Hz), 54.21.

Peroxymonosulfuric acid (Caro's Acid): Finely ground ammonium persulfate (11.6 g, 51 mmol) was added in 3 equal portions over a period of several minutes to an ice cold solution of concentrated sulfuric acid (32 N, 8 mL, 2.85 equiv) and ice water (1.7 mL, 1. 85 equiv). The solution was brought to room temperature and stirred until a clear homogeneous solution was obtained. In many instances, gentle heating aided in the dissolution of the persulfate. The solution thus obtained was used for the following preparation.

Pentafluorosulfanyl methyl acetate (2.3): A flask containing 1,1-dimethoxy-2-(pentafluorosulfanyl)ethane in 10 mL of anhydrous methanol was fitted with a pressure equalizing dropping funnel containing 6 mL (2 equiv) of the peroxymonosulfate (Caro's Acid). The peroxymonosulfate solution was added dropwise to the stirred solution of the acetal and the solution was allowed to stir overnight at 45°. The solution was treated with 5% sodium bicarbonate to quench the acid and the solution was partitioned with diethyl ether (20 mL). The layers were separated and the ether layer was washed with with 10 ml of $NaHCO_3$ followed by 10 mL of water. The combined aqueous layers were back extracted with diethyl ether (10 mL) and the ether layers were combined and dried with magnesium sulfate. Solvent was removed under reduced pressure to provide 1.29 g of the ester in 63% yield. ^{1}H NMR ($CDCl_3$): δ 6.89 (pentet, 2H, J=7.8 Hz); δ 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 163.018, 70.34 (pentet, J=17.25 Hz), 53.51. ^{19}F NMR ($CDCl_3$): δ 78.94 (pentet, 1F, J=143.5 Hz); δ 70.8 (doublet of mult, 4F, J=147.7 Hz). FTIR (cm^{-1}): 2964 (w), 1756.2 (s), 1442.7 (m), 1319.0 (m), 1268.5 (m), 1166.4 (s), 1020.4 (m), 868.8 (bs), 709.7 (m), 657.9 (m). MS (low resolution): m/z 169 ($C_2H_2OSF_5$); m/z 127 (SF_5); m/z 89 (SF_3); m/z 56; m/z 41 (C_2HO); m/z 28 (CO).

4-(pentafluorosulfanyl) methyl but-2-enoate (2.6): A solution of 3-chloro-4-(pentafluorosulfanyl) methyl butanoate (**2.9**) in methanol was prepared and one equivalent of sodium methoxide/methanol solution was added dropwise slowly to result in a yellow solution. After stirring for one hour, the solution was partitioned with ether and water. The ether layer was washed with small portions of water and the ether layer was dried with magnesium sulfate, filtered, and the solvent was removed under reduced pressure to provide 0.43 g (76 %) of colorless liquid. ^{1}H NMR ($CDCl_3$): δ 7.0 (pentet,

1H, J=7.5 Hz); δ 6.09 (dt, 1H, J=15.6, 1.2 Hz); δ 4.38 (ddp, 2H J=7.5 , 0.9 Hz); 3.79 (s, 3H). ^{19}F NMR ($CDCl_3$): (AB_4) δ 80.53 (pentet, 1F, J=143.0 Hz); δ 65.87 (doublet of mult, 4F, J=143.0 Hz). ^{13}C NMR ($CDCl_3$): δ 165.5, 135.22 (pentet, J=4.5 Hz), 128.5, 71.57 (pentet, J=15.8 Hz), 52.25.

3-chloro-4-(pentafluorosulfanyl) methyl butyrate (2.9): A round bottom three-neck flask was flame-dried and fitted with a total reflux condenser, stir bar, septum, and a gas bubbler tube. The flask was charged with 30 mL of hexane and vinyl acetic acid methyl ester (2.2 g, 22.0 mmol) and was cooled with a dry ice/acetonitrile bath (-42 °C). Sulfur pentafluorochloride (4.3 g, 26.4 mmol, 1.2 equiv) was condensed into the solution via the gas bubbler over a period of a few minutes. The solution was allowed to stir for a few minutes and a catalytic amount of 1.0 molar triethylborane (2.2 mL, 2.2 mol, 0.1 equiv) was added. The solution was stirred for 20 minutes at -42 ° before warming to room temperature. The solution was passed through a short length of silica gel and solvent was removed under reduced pressure to provide 4.06 g of clear liquid in 70% yield. ^{1}H NMR ($CDCl_3$): δ 4.75 (mult, 1H); δ 4.08 (mult, 2H); δ 4.34 (s, 3H); δ 3.0 (dd, 1H, J=16.6, 5.5 Hz); δ 2.85 (dd, 1H, J=16.3, 7.7). ^{19}F NMR ($CDCl_3$): (AB_4) δ 79.59 (p, 1F, J=146.6 Hz); δ 63.5 (dm, 4F, J=146.6 Hz). ^{13}C NMR ($CDCl_3$): δ 169.5; 147.46; 52.56; 50.5; 42.0.

2-acetoxy-2-chloro-1-(pentafluorosulfanyl) propane (2.10): A round bottom three-neck flask was flame-dried and fitted with a total reflux condenser, stir bar, septum, and a gas bubbler tube. The flask was charged with 40 mL of hexane and isopropenyl acetate (2.75 mL, 2.5 g, 25 mmol) and was cooled with a dry ice/acetone bath (-78 °C). Sulfur pentafluorochloride (5.0 g, 30.8 mmol, 1.23 equiv) was condensed into the

solution via the gas bubbler over a period of a few minutes. The solution was allowed to stir for a few minutes and a catalytic amount of 1.0 molar triethylborane (2.5 mL, 2.5 mol, 0.1 equiv) was added. The solution was stirred for 1 hour at -78 ° before warming to room temperature. The solution was passed through a short length of silica gel and solvent was removed to give 6.3 g (96 %) of 2-acetoxy-2-chloro-3-(pentafluorosulfanyl) propane. ^{1}H NMR ($CDCl_3$): δ 4.95 (dp, 1H, J=14.5, 8.5 Hz); δ 4.03 (dp, 1H, J=14.5, 8.0 Hz): δ 2.20 (s, 3H); δ 2.12 (s, 3H). ^{19}F NMR ($CDCl_3$): (AB_4) δ 77.84 (p, 1F, J=143.8 Hz); δ 64.68 (dm, 4F, J=143.8 Hz).

1-(pentafluorosulfanyl)-2-propanone (2.11): A mixture of the 2-acetoxy-2-chloro-1-(pentafluorosulfanyl) propane (2.9 g, 11.0 mmol) (**2.10**) in 10 mL of water was stirred thoroughly and 1 molar equivalent of potassium carbonate (15 mL, 5% w/v soln) was added dropwise to the solution. The resulting yellow solution disappeared within 10 minutes and the solution was refluxed for 1 hour. The solution was extracted with three 15 mL portions of dichloromethane. The combined dichloromethane extracts were combined, dried with magnesium sulfate, filtered, and solvent removed under reduced pressure to afford 1.5 g of liquid (74%). ^{1}H NMR ($CDCl_3$): δ 4.33 (p, 1H, J=8.0 Hz); δ 2.41 (s, 3H). ^{19}F NMR ($CDCl_3$): (AB_4) δ 76.86 (p, 1F, J=143.8 Hz); δ 68.3 (dm, 4F, J=146.6 Hz).

2-hydroxy-2-phenyl-1-(pentafluorosulfanyl) propane (2.12): Bromomagnesium benzene was prepared by dropwise addition of a solution bromobenzene (0.33 mL) in THF (10 mL) to a flask containing 0.0728 g of magnesium in 5 mL of THF and a catalytic amount of iodine. After 1 hour, the charcoal grey solution was treated with the pentafluorosulfanyl 2-propanone (0.4986 g, 2.7 mmol) to result in a slight yellow

solution. After stirring for 1 hour, the solution was quenched with 10% ammonium chloride solution washed with three 5 mL portions of water. The ether layer was dried with magnesium sulfate, filtered, and concentrated to give the title compound. ^{1}H NMR ($CDCl_3$): δ 7.5-7.15 (m, 5H); δ 4.26-3.9 (m, 2H); δ 1.73 (s, 3H). ^{19}F NMR ($CDCl_3$): δ 85.12 (p, 1F, J=143.8 Hz); δ 70.19 (dt, 4F, J=146.4, 8.74 Hz). ^{13}C NMR ($CDCl_3$): δ 144.69; 128.81; 127.89; 124.65; 81.71 (p, J=5 Hz), 75.25; 30.07.

General procedure for the addition of pentafluorosulfanyl bromide to alkenes and alkynes: A three-neck round bottom flask was flame dried and equipped with a stir bar, total reflux condenser and 1/8" Teflon tubing gas inlet tube. The solvent (30 mL) and the alkyne or alkene was introduced into the flask and the solution was cooled to –78° C. Pentafluorosulfanyl bromide was condensed into the solution through the Teflon tube inlet. The solution was allowed to stir for several minutes at – 78° before adding 0.1 equiv of triethylborane to initiate the reaction. The reaction mixture was stirred for 1 hour at – 78° C before warming to room temperature. Passing the solution through a short length of silica gel and removal of the solvent provide the alkene or alkane in varying yields (Table 2-3).

2-bromo-1-(pentafluorosulfanyl)octane (2.15): ^{1}H NMR ($CDCl_3$): δ 4.46-4.36 (m, 1H); δ 4.28-3.92 (m, 2H); δ 2.1-1.96 (m, 1H); δ 1.9-1.76 (m, 1H); δ 1.4-1.2 (m, 11H). ^{19}F NMR ($CDCl_3$): δ 82.85 (p, 1F, J=148.1 Hz); δ 65.44 (dt, 4F, J=144.7, 8.46 Hz). HRMS (EI): Calculated for $C_8H_{16}SF_5Br$: 318.007622, found 318.0067 (monoisotopic).

2-Bromo-1-(pentafluorosulfanyl)hexane (2.16): ^{1}H NMR ($CDCl_3$): δ 4.46-4.38 (m, 1H); δ 4.3-3.92 (m, 2H); δ 2.12-1.98 (m, 1H); δ 1.9-1.76 (m, 1H); δ 1.66-1.22 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 77.4 (mult), 47.18 (mult, J=4.2), 37.83, 29.5, 22.0, 14.05. ^{19}F

NMR ($CDCl_3$): δ 82.8 (p, 1F, J=144.67 Hz); δ 65.4 (dt, 4F, J=8.7, 146.4 Hz). HRMS (EI): calculated for $C_6H_{12}SF_5Br$: 289.976323, found 289.9763 (monoisotopic).

4-bromo-5-(pentafluorosulfanyl)oct-4-ene (2.17): ^1H NMR ($CDCl_3$): δ 2.82 (t, 2H, J=7.8 Hz); δ 2.63 (t, 2H, J=7.8 Hz); δ 1.74-1.57 (mult, 4H); δ 0.95 (td, 6H, J=7.5, 2.49 Hz). ^{19}F NMR ($CDCl_3$): δ 86.25 (pentet, 1F, J=149.5 Hz); δ 67.40 (d, 4F, J=149.5 Hz). HRMS: Calculated for $C_8H_{14}SF_5Br$: 315.991973, found 315.9920 (monoisotopic).

2-bromo-1-(pentafluorosulfanyl)heptane (2.18): ^1H NMR ($CDCl_3$): δ 4.46-4.34 (m, 1H); δ 4.3-3.9 (m, 2H); δ 2.1-1.96 (mult, 1H); δ 1.92-1.74 (m, 1H); δ 1.66-1.4 (m, 2H); δ 1.38-1.2 (m, 7H). ^{19}F NMR ($CDCl_3$): δ 82.83 (pentet, 1F, J=148.1 Hz); δ 67.40 (dt, 4F, J=146.6, 8.46 Hz).

1-bromo-2-(pentafluorosulfanyl)styrene (2.19) : ^1H NMR ($CDCl_3$): δ 7.5-7.28 (mult, 5H); δ 7.09 (pentet, 1H, J=7.8 Hz). ^{19}F NMR ($CDCl_3$): δ 86.46 (pentet, 1F, J=149.7 Hz); δ 67.40 (d of mult, J=151.43 Hz). HRMS: Calculated for $C_8H_6SF_5Br$ 307.929359, found 307.9294 (monoisotopic).

2-bromo-1-(pentafluorosulfanyl)cyclohexane (2.20): Mixture of isomers. ^1H NMR ($CDCl_3$): δ 4.59 (td, 1H, J=); δ 4.43 (td, 1H, J=); δ 4.1 (mult, 2H); δ 2.4-2.1 (mult, 4H); δ 1.9-1.2 (mult, 12H). ^{19}F NMR ($CDCl_3$): δ 85.19 (pentet, 1F, J=142.97 Hz); δ 56.9 (dd, J=141.28, 3.38 Hz).

1-Acetoxy-2-propyne (2.21): A solution of the alcohol (6 mL, 5.78 g, 0.103 mol) and acetic anhydride (16.2 g, 0.159 mol, 1.5 equiv) in 70 mL of dichloromethane was prepared. To this stirred solution was added triethylamine (15 mL, 1 equiv). The solution was stirred for 3 hours at room temperature, washed with two 20 mL portions of 15% potassium hydroxide and one 15 mL portion of 5% hydrochloric acid. The organic

layer was dried with magnesium sulfate, filtered, and concentrated under reduced pressure. Distillation provided a 3.6 g (35 %) clear liquid boiling between 123-126 °C.

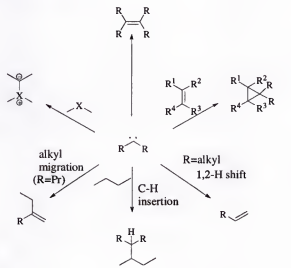
3-acetoxy-2-bromo-1-(pentafluorosulfanyl)prop-1-ene (2.22): Prepared according the general procedure. ^{1}H NMR (CDCl3): δ 6.93 (pentet, 1H) ; δ 5.02 (s, 2H); δ 2.12 (s, 3H). ^{13}C NMR (CDCl3): δ 169.96; 141.19 (pentet, J_{CF}=21.53 Hz); 131.7 (t, J_{CBr}=6 Hz); 62.81; 20.60. ^{19}F NMR (CDCl3): δ 79.8 (pentet, 1F, J=154.8 Hz); δ 67.0 (d, J=151.7 Hz). HRMS (EI): Calculated for $C_5H_6O_2SF_5Br$ 303.919203, found 304.9275 (M+H).

2-Bromo-1-(pentafluorosulfanyl)styrene (2.23): Prepared according to the general procedure. ^{1}H NMR (CDCl3): δ 7.46-7.28 (mult, 5H) ; δ 7.1 (p, 1H, J=7.5 Hz) ^{19}F NMR (CDCl3): δ 80.47 (pentet, 1F, J=155.95 Hz); δ 67.4 (d, J=153.1 Hz). ^{13}C NMR (CDCl3): δ 135.38 (dp, J=20.25, 1.73 Hz); 132.7; 127.8 (pentet, J=6.6 Hz); 125.2; 123.73; 122.82 (p, J=1.65 Hz).

CHAPTER 3
REACTIONS OF DIFLUOROCARBENE WITH ETHERS AND RELATED HETEROATOMIC COMPOUNDS

3.1 Introduction

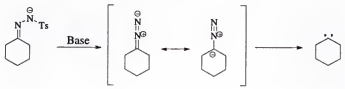
Despite the short lifetimes of carbene intermediates, this field of chemistry is rich due to the diversity of the reactions which carbenes are capable of undergoing (Scheme 3-1). Carbenes are extremely useful for the preparation of three-membered ring system through a [2+1] cycloaddition process with alkenes. Due to the high reactivity of carbenes, they are capable of undergoing a host of reactions which would otherwise be difficult to accomplish by other methods. Scheme 3-1 illustrates the reactions of generic carbenes. In addition to undergoing C-H insertion reactions and alkyl migrations, carbenes are very useful as a one carbon synthon for the formation of cyclopropanes and three-membered heterocyclic rings.



Scheme 3-1: Reactions of carbenes.

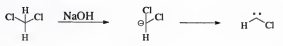
3.1.2. Generation of Carbenes and Difluorocarbene

A number of reagents have been developed as carbene precursors. Perhaps the oldest and most extensively used method for the generation of carbenes relies upon the photolysis of the diazo or diaziridene precursor. The simplest member of the carbene family, methylene carbene, may be prepared by photolysis of the parent compound diazomethane prepared from treatment of N, N'-dimethyl-N, N'-dinitrosoterephthalamide with sodium hydroxide.[64] Tosylhydrazones, prepared from the condensation of tosylhydrazine with a carbonyl compound, are another route to carbenes.[65] The formation of the carbene procedes through a diazonium intermediate as shown in equation 3-1 followed by α-elimination.



(3-1)

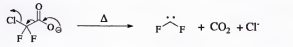
There are few other general methods that exist for the formation of carbenes. In 1958, Simmons and Smith reported on the formation of cyclopropanes by using the carbenoid formed from diiodomethane and a zinc-copper couple.[66] The use of rhodium catalysts to generate the carbenoids from diazo precursors has been applied to organic synthesis of complex molecules, notably by Padwa's research group.[67] Halogenated carbenes are often prepared by deprotonation of the carbene center followed by the alpha elimination of a halogen (eq 3-2).[68]



(3-2)

Due to the unique properties of fluorine imparted by the high electronegativity of the element and the ever-increasing importance of a cyclopropyl group in synthesis, the formation of fluorocarbenes is of importance. A small number of methods for accomplishing the synthesis of gem-difluorocyclopropanes using difluorocarbene have been developed. Seyferth's laboratory developed a number of carbene reagents based on the decomposition of mercury (II) compounds[69] to give a variety of dihalocarbenes and trimethyl(trifluoromethyl)stannanes[70] to give difluorocarbene. More recent methods for the generation of difluorocarbene have sidestepped the toxic nature of mercury. Burton's use of bromodifluoromethylphosphonium bromide[71] and the Dolbier-Conrad modification of the Simmons-Smith reaction[72] provide useful, easily prepared precursors for difluorocarbene.

Of particular interest with regard to the research discussed herein, is the generation of difluorocarbene through a series of degradations induced by the formation of a carboxylic anion. It has long been known that difluorocarbene may be generated from the thermal degradation of the chlorodifluoroacetic acid sodium salt (**3.1**, eq 3-2).[73]

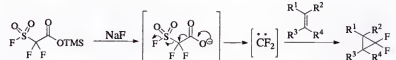


(3-2)

3.1

This approach to generating difluorocarbene has been utilized by other researchers as well. Wheaton and Burton synthesized gem-difluorocyclopropanes by using the methyl ester of **3.1** by deprotecting the methyl ester with LiCl in a polar aprotic solvent.[74] Chen and Wu during the course of work with perfluoroalkyl sulfonates found that difluorocarbene could be generated from fluorosulfanyl difluoroacetic acid under basic conditions.

Dolbier and coworkers have described the synthesis of gem-difluorocyclopropanes using trimethylsilyl fluorosulfanyldifluoromethylacetate (TFDA, **3.2**, eq 3-3) as the carbene precursor.[75,76] A catalytic amount of metal fluoride (e.g. NaF) is used to initiate the cleavage of the trimethylsilyl protecting group. The use of the ester is advantageous as all of the fluoride generated during the reaction is consumed maintaining the catalytic cycle. Thus, the formation of the trifluoromethyl anion and subsequent reactions are minimized.

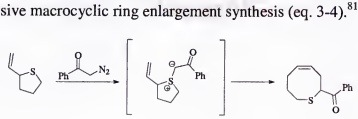


3.2 (3-3)

3.1.3. Sulfonium and Oxonium Ylides via Carbenes

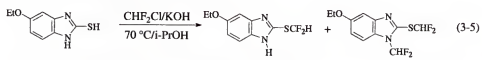
The reaction of a carbene with the unpaired valence electrons of a heteroatom, allow for the formation of ylide intermediates. In some cases, the ylide may be suitably stable enough to be isolated. Such is the case with many ylides of phosphorus, nitrogen, and sulfur. However, oxonium ylides are not stable and exist only as intermediates in reactions.

Ylides such as N-heterocyclic carbenes, since their development by Arduengo in 1991[77-79], have found important applications as ligands in metathesis reactions, for catalyzing reactions, and as participants in multicomponent reactions.[80] Further, sulfur ylides have found usefulness in 2,3-sigmatropic reactions as demonstrated by Vedejs for the successive macrocyclic ring enlargement synthesis (eq. 3-4).[81]



(3-4)

The formation and reactions of fluorinated ylides have been described in the literature for the formation of heterocyclic compounds such as pyrrolines[82] and pyrrolidinones[83] through [3+2] dipolar cycloadditions with alkenes. Difluorocarbene has been demonstrated to react with mercaptoazoles to generate a difluoromethylide intermediate which then undergoes rearrangement to give the S-difluoromethyl substituted products as shown in equation 3-5.[84]



(3-5)

Given the propensity of ylide intermediates to undergo sigmatropic and other rearrangements to give difluoromethylene and difluoromethyl products respectively, it would be of interest to investigate reactions between heteroatom-containing compounds and difluorocarbene generated using the novel reagent TFDA and closely examine the products from the reaction. In this manner, the reactivity of the difluorocarbene generated from TFDA could be determined from the distribution of products (e.g. CH insertion, [2, 3]-sigmatropic reaction, cyclopropanation).

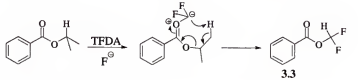
3.2 Examination of Difluorocarbene Reactions with Heteroatomic Compounds

Despite previous studies showing the utility of TFDA as a difluorocarbene reagent for the formation of gem-difluorocyclopropanes, the propensity of this reagent to induce rearrangements and other reactions associated with the formation of ylides had not been described in the literature at this time. Research conducted by Dr. Xiao Hong Cai within the laboratory of Professor Dolbier had previously shown that TFDA reacted with ketones in an unexpected fashion to provide products from the rearrangement of ylide intermediates.[85] Critical to this reaction was the use of TFDA that was completely free of the acid precursor. Although most of the acid impurity of TFDA can be easily removed

by distillation, the easily cleavable silyl group ensured the ubiquitous presence of the acid in small amounts. Removal of small amounts of the acid (ca. 1-2 %) could be accomplished by treating TFDA with equimolar amounts of triethylamine.

Consideration of substrates for reactions with difluorocarbene was made based the heteroatom and the groups attached to the heteroatom center. Our initial goal was to investigate the potential formation of onium ylides using acid-free TFDA, and subsequent rearrangements with the anticipation of forming the difluoromethyl ester (**3.3**) in appreciable yield from isopropyl benzoate through the rearrangement resulting from a seven-membered transition state depicted in equation 3-6.

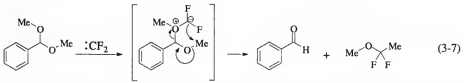
An aliquot of a solution of the benzoate ester and catalytic sodium fluoride in toluene that had been treated with two equivalents of TFDA was subjected to proton and fluorine NMR. Careful examination of the mixture revealed none of the expected product for which the proton of the difluoromethyl moiety should be clearly evident as a triplet with a large coupling constant due to the geminal fluorines. The lack of formation of the product was not especially surprising given the unfavorable seven-member transition state required for the formation of the product.



3.3 (3-6)

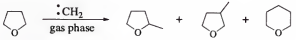
To circumvent the problems associated with the seven-member transition state, other substrates were subjected to the same conditions. The tert-butyl benzoate ester with the increased steric bulk was predicted to force a proton on a methyl group in the vicinity of the anionic center of the ylide. The triethyl orthoester was also chosen as a substrate since the presence of three oxygen atoms would increase the probability of forming the

oxonium ylide. In the reaction of benzaldehyde dimethyl acetal, trace amounts of unknown compounds were formed but the majority of the product was benzaldehyde (eq 3-7). A closer inspection of this reaction aimed at elucidating the mechanism for the apparent deprotection was conducted by using a low-temperature U-tube to trap volatile materials. It was anticipated that the formation of 2,2-difluoroethyl methyl ether would be formed through the intramolecular rearrangement-elimination depicted in equation 3-7. Surprisingly, this product was not detected in the trap. Trimethylsilyl fluoride formed from the catalytic initiation of TFDA is the only significant product. Presumably, upon formation of the ylide, external nucleophilic attack by an unknown species leads to the deprotection of the acetal.



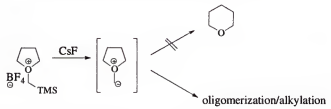
(3-7)

All of these reactions, with exception of the benzaldehyde dimethyl acetal, aimed at forming products related to carbene reactions, particularly with respect to the formation of the difluoromethyl ester in the case of the tert-butyl ester, failed to give the expected products. The failure of these reactions to form products containing the difluoromethylene moiety can be rationalized on the basis of the stability of the ylide intermediate. The electrophilicity of the difluorocarbene should favor the formation of the ylide but the short lifetime expected at the high temperatures for the onium ylide and the stabilization of the negative charge by the geminal fluorines probably preclude further reactions from occurring in these systems.



(3-8)

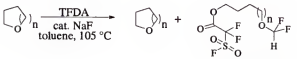
Rearrangement products resulting from onium ylides of cyclic ethers were observed in the reaction of tetrahydrofuran with methylene carbene in the gas phase by Frey and Voissey (eq 3-8).[86] When the reaction is conducted in the liquid phase by photolysis of diazomethane, less than two percent of the ring-enlarged product resulting from the Stevens rearrangement of the ylide is noted. Olah and his laboratory attempted the formation of pyran by desilylation of the tetramethylene((trimethylsilyl)methyl)-oxonium tetrafluoroborate with cesium fluoride (eq 3-9).[87] The ylide generated in this manner was expected to undergo a Stevens rearrangement to give the pyran. However, they were unable to detect any such product formed from the reaction instead the products formed were oligomers and alkylated products.



(3-9)

More successful reactions of ylides derived from cyclic ethers have been reported by Kirmse who found that methylidene oxetane proceeds to give ring-opened products resulting from proton elimination, rearrangement, and nucleophilic attack by the solvent (eq 3-10).[88] Solvent participation and the electronic nature of the ylide have been a subject of study for Oku who found that ring-opening by an elimination versus nucleophilic attack are affected by the solvent.[89] Rearrangement of the ylide formed from photolysis of methyl diazophenylacetate and tetrahydrofuran conducted in methanol primarily gave the ring-opened elimination product. Upon conducting the photolysis in acetic acid, ring-opening resulted from nucleophilic attack by acetate ion.

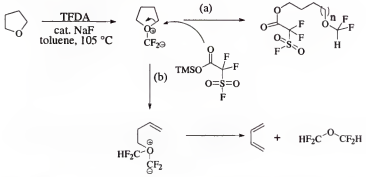
We believed that performing reactions using cyclic ethers with difluorocarbene generated at 110° C using TFDA might similarly lead to the ring-opened products resulting from intramolecular proton abstraction at the 3-position of the tetrahydrofuran ring in addition to other products (eq 3-10). When a solution of tetrahydrofuran or tetrahydropyran was subjected to an excess of acid-free TFDA no terminal alkenes were detected in an aliquot of the solution. However, the formation of products was clearly evident from the proton and fluorine NMR. Purification of the major species present in the mixture by chromatography of the reaction mixture provided low yields of the product shown in equation 3-11.



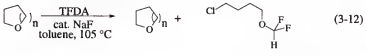
3.4, n=1, 16%
3.5, n=2, 10%

Clearly under the conditions of the reaction of acid-free TFDA the formation of the products must arise from nucleophilic attack of the putative ylide by the acid anion or, more likely, by the TMS ester. The formation of the difluoromethyl group is not so evident given the lack of acidic protons in the reaction mixture and the notable absence of alkene species. One possible explanation for the proton source is the tetrahydrofuran which comes from successive proton eliminations to generate butadiene which would be removed as a gas (Scheme 3-2). It was also discovered inadvertently during the course of this research that other nucleophilic species can generate products derived from the ring opening of the ylide. TFDA which contained a small amount of trimethylsilyl chloride to esterify any acid residue had been employed for some of the reactions with cyclic

ethers. Workup of the reaction mixtures using TFDA/trimethylsilyl chloride solution provided ring-opened products resulting from nucleophilic attack by chloride ion (eq 3-12). In this reaction, protonation of the difluoromethylene anion is likely due to the hydrogen chloride present in the TFDA.

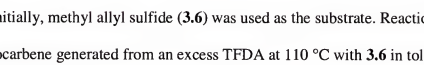


Scheme 3-2: Potential mechanism for formation of difluoromethyl ethers.



(3-12)

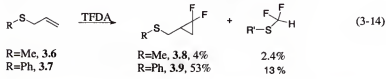
As a part of the study of difluoromethylene ylides we wanted to investigate the reactions of sulfides with difluoromethylene. Considering that ylides derived from allyl thioethers have been demonstrated to undergo a sigmatropic rearrangement[90] as shown in equation 3-13, we believed that the formation of the difluoromethylide deriving from a sulfide bearing an allylic moiety would be of interest. Although the double bond could undergo cyclopropanation it was hoped that it would undergo a 2,3-sigmatropic rearrangement to provide the gem-difluoro sulfide.



(3-13)

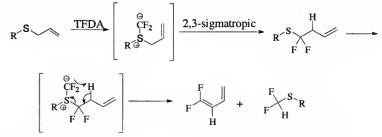
Initially, methyl allyl sulfide (**3.6**) was used as the substrate. Reaction of difluorocarbene generated from an excess TFDA at 110 °C with **3.6** in toluene gave no

products related to sigmatropic rearrangements nor significant amounts of the C-H insertion product. Surprisingly, the formation of gem-difluoro-cyclopropane was formed only in a small amount as evidenced by a characteristic pattern in the fluorine NMR. In addition to the cyclopropane, the slight formation of a compound bearing a difluoromethyl group was evident from a signal in the proton and fluorine NMR for such a group. The formation of the difluoromethyl thioether was puzzling since the origin of the proton was not obvious.



(3-14)

In an effort to eliminate potential proton sources and give preference for the ylide to undergo a sigmatropic rearrangement, the reaction was repeated using phenyl allyl sulfide (**3.7**). This reaction provided the cyclopropane (**3.9**) in 53% NMR yield and 13% of an unknown product bearing a difluoromethyl thiol substituents presumed to be S-difluoromethyl thiobenzene. A mechanism analogous to the one outlined in Scheme 3-2 (pathway b) can be used to explain the formation of difluoromethyl thiol ethers.



Scheme 3-3: Possible mechanism for the formation of difluoromethyl thioethers.

3.3 Conclusions

The formation of difluorocarbene from TFDA has been shown to be an effective method for the synthesis of gem-difluorocyclopropanes. The reaction of

difluoromethylene generated in this manner was expected to react with isopropyl benzoate and tert-butyl benzoate to provide difluoromethyl esters through the rearrangement of the ylide intermediate. Disappointly, these results were not realized; the failure of the ylide to rearrange most likely was a result of the unfavorable seven-membered transition state and the stability of the anionic center. The dimethyl acetal of benzaldehyde, however, underwent deprotection in the presence of difluoromethylene to give the parent aldehyde.

The formation and reaction of oxonium ylides were attempted using tetrahydrofuran and pyran. The ylide intermediates preferentially give ring-opened products resulting from nucleophilic attack rather the terminal alkenes resulting from proton abstraction. Ylides formed from the allylic sulfides give trace amounts of difluoromethyl sulfides and gem-difluorocyclopropanes but no products resulting from 2,3-sigmatropic rearrangements.

3.4 Experimental

General experimental procedures: Commercial reagents were used without further purification unless otherwise noted. All NMR spectra were obtained using a 300 Mhz Varian instrument using $CDCl_3$ as a lock solvent and reference unless explicitly stated otherwise. Fluorobenzene was used as an internal standard to determine NMR yield. Mass spectral data was acquired on a Finnigan MAT 95Q hybrid-sector mass spectrometer (ThermoFinnigan, San Jose, CA) by the mass spectral laboratory services at the University of Florida. Electron Ionization (EI) was carried out at 70 eV using a direct insertion probe. Chemical Ionization (CI) was carried out at 150 eV using a direct insertion probe in the presence of methane.

Tetrahydrofuran was dried over benzophenone ketyl radical and freshly distilled prior to use. Toluene used as the solvent for the carbene reactions was distilled onto activated 4 Å molecular sieves. TFDA was distilled as necessary. Residual acid was otherwise removed by treating the TFDA with 1 equivalent of anhydrous triethylamine immediately prior to use. All glassware was thoroughly flame-dried prior to use under a nitrogen atmosphere.

General procedure for TFDA reactions: A 15 mL 2-neck round-bottom flask was thoroughly flame-dried and was equipped with a stir bar and condenser. Dry toluene (3 mL), a catalytic amount of sodium fluoride, and the ether (10 mmol) were added to the flask. The solution was heated to gentle reflux and TFDA (1.1-2 equiv) was introduced via syringe pump through a rubber septum over several hours.

1-(Fluorosulfanyl)difluorosulfanylacetic acid-4-difluoromethoxybutyl ester (3.4): Purified by column chromatography (25% ethyl acetate/hexanes). ^{1}H NMR ($CDCl_3$): δ 6.2 (t, 1H, J=74.4 Hz); 4.51 (t, 2H, J=6.6 Hz); 3.9 (t, 2H, J=6.0 Hz); 1.95-1.86 (m, 2H); 1.87-1.72 (m, 2H. ^{19}F NMR ($CDCl_3$): δ 40.81 (s, 1F); -84.68 (d, 2F, J=74.45 Hz); -103.8 (s, 2F). LRMS (EI): m/z 71 (100); 78 (25); 204 (18).

1-Fluorosulfanyl)difluorosulfanylacetic acid-5-difluoromethoxypentyl ester (3.5): Purified by column chromatography (5% ethyl acetate/hexanes). ^{1}H NMR ($CDCl_3$): δ 6.19 (t, 1H, J=74.4 Hz); 4.51 (t, 2H, J=6.6 Hz); 3.9 (t, 2H, J=6.0 Hz); 1.95-1.86 (m, 2H); 1.87-1.72 (m, 2H. ^{19}F NMR ($CDCl_3$): δ 40.81 (s, 1F); -84.68 (d, 2F, J=74.45 Hz); -103.8 (s, 2F).

2,2-Difluorocyclopropylmethyl phenyl sulfide (3.9): Purified by column chromatography (5% ethyl acetate/hexanes, R_f=0.25). ^{1}H NMR ($CDCl_3$): δ 7.42-7.18 (t,

5H); 3.05 (dd, 1H, J=13.6 ,6.8 Hz); 2.88 (ddd, 1H, J=13.4, 7.8, 1.0 Hz); 1.9-1.7 (m, 1H); 1.54-1.38 (m, 1H); 1.4-1.0 (m, 1H). ^{19}F NMR ($CDCl_3$): δ -128.4 (dtt, 1F, J=157.6, 12.7, 2.5 Hz); -128.68 (tt, 1F, J=9.1. 3.95 Hz); -143.78 (ddd, 1F, J=157.9, 5.1, 13.0 Hz).

CHAPTER 4
HYPERVALENT IODOSYL COMPOUNDS—DISCRIMINATION BETWEEN ARYL GROUPS CONTAINING FLUORINATED AROMATIC SUBSTITUENTS

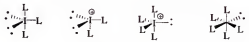
4.1 Introduction to Hypervalent Iodine Compounds

The chemistry of hypervalent iodine compounds has been a long-known and is well-documented in the literature. The synthesis of dichloro(iodo)-λ^3-benzene by oxidation of iodobenzene with chlorine gas was performed by Willgerodt in 1886 and marked the birth of hypervalent iodine chemistry.[91,92] The potential for the formation of hypervalent compounds exists only for compounds containing elements of groups 15-18 that have an unoccupied valence d-orbital since these atoms can accommodate more than the usual octet of valence electrons. Hence, elements of the third period and below are capable of becoming hypervalent centers in atoms. Notably, such hypervalent compounds typically contain sulfur, phosphorus, and iodine. Compounds of iodine have proved to be particularly useful in the realm of synthetic chemistry as some are excellent oxidizing agents while other hypervalent iodine compounds display hypernucleofugacity. The role of the hypervalent compound is determined by the ligands to be discussed briefly in the following sections.

4.1.2 Nomenclature and Nucleofugacity of Iodanyl Compounds

Iodine as a hypervalent center is most commonly observed in the +3 and +5 oxidation states. In terms of these two oxidation states, there are four arrangements for the bonding ligands around the iodine center (Scheme 4-1). These bonding arrangements can be conveniently summarized by a nomenclature system introduced by Martin and

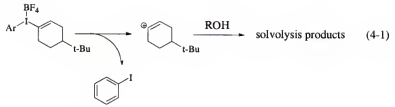
Arduengo in which the number of valence electrons, N, the hypervalent center, X, and the number of ligands, L, are used to describe the compound.[93] The examples shown in Scheme 4-1 are representative of the common hypervalent iodine (III) and (V) oxidation states and the Martin-Arduengo nomenclature is listed beneath each structure.



Martin-Arduengo Designation	10-I-3	8-I-2	10-I-4	12-I-5

Scheme 4-1: Nomenclature for common hypervalencies of iodine.

Compounds of the type 10-I-3 and 8-I-2 are denoted as λ^3-iodanes and are frequently encountered in organic synthesis. In particular, the ligands determine the overall properties of the hypervalent compound. Bonding to the central iodine atom is possible through hetero- or carbon atoms. The former compounds are strong oxidizing reagents while compounds bearing two carbon-iodine bonds often behave as ligand transfer reagents. Aryl iodanes often undergo reductive elimination to give the monovalent iodine which can be attributed to the increased partial positive charge on the iodine and the weak carbon apical bond. The leaving group abilities for alkyl-(aryl)iodanes such as those shown in eq 4-1 are about 10^6 greater than the triflate group. This extraordinary leaving group ability has been termed hypernucleofugacity. The pseudo first-order rate constants for the solvolysis of the (1-cyclohexenyl) aryliodane shown in eq 4-1 were calculated to be 0.229×10^4 s^{-1} at 35 °C.[94] A comparison of relative leaving groups is more instructive in displaying the awesome capability of hypervalent aryliodonium compounds as a leaving group. The relative rates for solvolytic reactions phenylethyl esters and halides in 80:20 ethanol: water are compared with the solvolyses of Table 4-1.



(4-1)

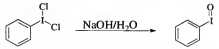
The data given in Table 4-1 clearly reflect the capability of iodonium salts to undergo a reductive elimination. Hence, hypervalent iodonium compounds are versatile reagents in organic synthesis.

Table 4-1: Leaving group abilities relative to chloride ion for solvolysis in 80:20 ethanol:water of 1-phenylethyl esters and halides.[95]

Nucleofuge	k_{rel}	Nucleofuge	k_{rel}
AcO	1.4×10^{-6}	MsO	3.0×10^{4}
Cl	1	TsO	3.7×10^{4}
Br	1.4×10^{1}	TfO	1.4×10^{8}
I	9.1×10^{1}		

4.1.3. Preparation of Hypervalent Iodine Compounds

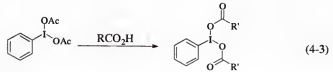
Willgerodt first prepared hypervalent iodine compounds by treatment of iodobenzene with chlorine to give the dichloroiodobenzene.[92] The iodobenzene dichloride can be used as a starting material to prepare other hypervalent compounds such as the iodosylbenzene shown in equation 4-2.[96,97]



(4-2)

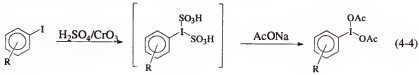
A large number of compounds have been synthesized using peracid to effect the oxidation of iodobenzenes. The classical method for the oxidation of iodobenzene to iodobenzene diacetate is performed by treating iodobenzene with commercial peracetic

acid.[98] This method can be adapted to provide other (dicarboxy)iodanyl compounds. The extreme lability of the acetate ligands provides another pathway for the synthesis of dicarboxy derivatives of iodosobenzene as demonstrated by Stang and coworkers equation 4-3.[99]



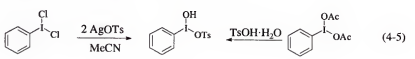
4-2 (4-3)

Another method for the synthesis of (diacetoxy)iodobenzenes involves the synthesis of the intermediate hydrosulfate (**4-3**, eq 4-4) followed by ligand exchange with acetate ion.[100] In this method a number of (diacetoxy)iodoarenes with deactivating substituents such as the para-NO_2, -Cl, and –Br were prepared.



4.3 (4-4)

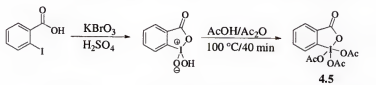
Perhaps one of the best known hypervalent iodine reagent besides (diacetoxy)iodobenzene is hydroxyl(tosyloxy)iodobenzene better known as Koser's reagent or HTIB (**4.4**, eq 4.5). The formation of HTIB is easily accomplished by treating the diacetoxy compound with toluenesulfonic acid monohydrate[101] or alternatively by treating the (dichloro)iodobenzene with silver tosylate.[102]



4.4 (4-5)

A large number of cyclic iodanes have been prepared and have proven valuable for the oxidation of organic compounds. The most notable of these, being the Dess-Martin periodane (**4.5**, eq 4-6), was originally prepared through the potassium bromate-mediated

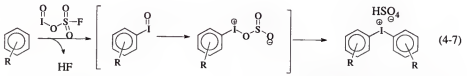
oxidation of the *ortho*-iodobenzoic acid followed by treatment of the intermediate hydroxyiodinane oxide with acetic anhydride at 100 °C for 40 minutes.[103] Most other methods for the conversion of the acid to the 12-I-5 iodinane are modifications of the original procedure. For example, it was shown that the transformation of the intermediate hydroxyiodinane oxide (IBX) to the DMP (Dess-Martin periodinane) ester proceeded in high high yield under milder, more efficient conditions.[104]



(4-6)

4.5

The preparation of alkenyl, alkynyl, and diaryliodonium salts is another important aspect of hypervalent iodine chemistry. Many of these compounds are readily prepared in good yields by coupling of arylboronic acids[105], arylsilanes[106], or arylstannanes with iodanylarenes. Zhdankin and coworkers found that iodosyl fluorosulfate was a highly efficient reagent for the synthesis of substituted diaryliodonium salts shown in eq 4-7.[107] Even strongly deactivating substituents such as the nitro moiety were tolerated by this reagent.



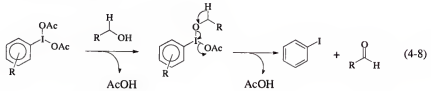
(4-7)

R=H, *p*-Cl, *p*-Br, *p*-F, *p*-Me, *p*-^{t}Bu, *m*-NO_2

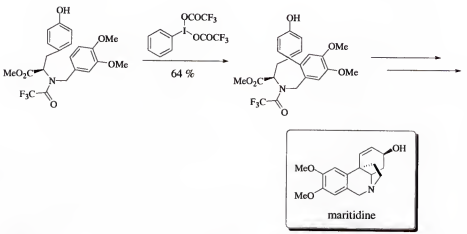
4.1.4. Reactions of Hypervalent Iodine Compounds

A thorough review of the reactions of hypervalent iodine compounds is beyond the scope of this dissertation. However, some of the most common reactions will be introduced to acquaint the reader with this chemistry. Most of the reactions encountered result from the highly electrophilic character of hypervalent iodine compounds and the

ability to undergo facile reductive elimination. The reactivity of iodine (III) compounds is determined by the type of ligands attached to the iodine center. Heteroatom ligands are necessary for the oxidation of organic compounds since the first ligand must undergo displacement and subsequent reduction; the second ligand takes place in the reductive elimination step (eq 4-8). The oxidation of alcohols to the ketone or the aldehyde can often be accomplished under mild conditions using λ^3-iodanyl compounds such as (dicarboxy)iodobenzenes or Dess-Martin periodinane. The oxidative ability of iodanyl compounds such as bis(trifluoroacetate)iodobenzene has been applied toward the synthesis of natural products such as the *Amaryllidacae* alkaloids (Scheme 4-1) through an oxidative arene coupling.[108]



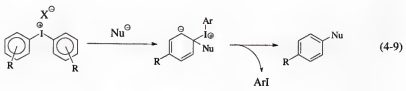
(4-8)



Scheme 4-1: Synthesis of alkaloid precursors using PIFA.

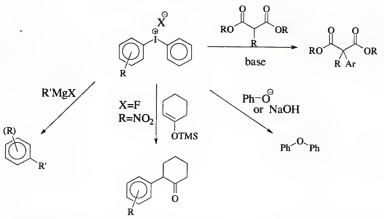
The synthetic utility of λ^3-iodanyl compounds is not strictly limited to the oxidation of alcohols and phenols. Hydroxy(tosyloxy)iodobenzene, better known as Koser's

reagent,[109,110] as well as derivatives thereof[111] have been used for oxidative α-tosylation of ketones.



(4-9)

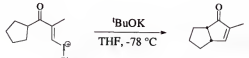
Diaryliodonium salts and other iodonium ions where the iodine is attached to two carbon atoms typically undergo nucleophilic additions followed by reductive displacement shown as an associative mechanism in equation 4-9. Examples of the versatility of diaryliodonium salts as an electrophilic arene source,[112-115] is shown in Scheme 4-2.



Scheme 4-2: Electrophilic reactions of diaryliodonium salts with nucleophiles.

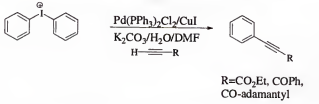
The exemplary leaving group ability of a phenyliodanyl group provides an electrophilic source of an alkene or alkyne using alkenyl-, and alkynyl(aryl)iodonium salts, respectively. In the case of the former, when the possibility exists for the formation of an α-anion, the alkene may undergo a reductive elimination to give alkylidene carbenes that further react to provide a variety of products based upon the structure of the starting material. In the example shown in equation 4-10, the intermediate carbene

generated from α,β−unsaturated compound reacts by C-H insertion to give the *cis*-fused [3.3.0]octane compound.[116]



4-10

A number of metal-catalyzed reactions such as the Sonogashira coupling, Suzuki,[117] Heck, and Takai[118] reactions have been extended to the preparation of arenyl compounds from diaryliodonium salts. Stang and coworker have demonstrated the superior reactivity by preparing a number of aryl alkynes from the Sonogashira coupling of electron-deficient alkynes with diaryliodonium salts as shown in equation 4-11.[119]



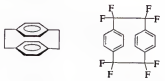
(4-11)

4.2 Examination of Fluorinated Hypervalent Iodine Systems

4.2.1 Attempt to Prepare Hypervalent Iodine Derivatives of 1,1,2,2,9,9,10,10-Octafluoro[2.2]paracyclophane

The unique structural features associated with the cyclophane family imparts unique chemical and physical properties to these structures due to the overlap of the p-orbitals of the aromatic rings and the steric strain for members with the shortest bridging alkyl groups. The member most often associated with this family is the [2.2]paracyclophane (**4.5**, Scheme 4-3) which was an inadvertent byproduct from a polymeric reaction.[120] Since that time, the synthesis of the bridge-fluorinated analogue of **4.5** has been achieved by Chow and coworkers (**4.6**) by dimerization of the xylylene intermediate formed at 600 °C.[121] Dolbier and coworkers have contributed significantly

to this area of chemistry and have provided useful syntheses for the 1,1,2,2,9,9,10,10-octafluoro-[2.2]paracyclophane and substituted derivatives (Scheme 4-4).[122-127]



4.5 **4.6** **4.7**

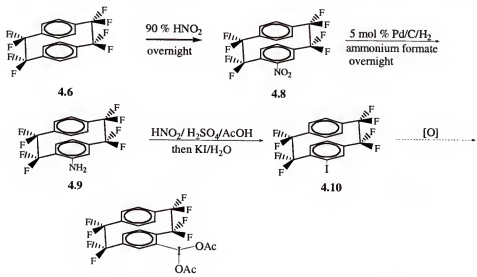
Scheme 4-3: Paracyclophane, AF4, and Parylene-HT

The 1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane (referred to as AF4) with the lack of oxidizable moieties and the strong C-F bonds on the bridging ethylene groups has attractive physical properties that would be particularly useful for the material and electronic industries. In addition, AF4 is the precursor of Parylene-HT polymer (**4.7**).

Given the useful nature of AF4 as a polymer precursor, there is considerable effort to develop syntheses for the derivatives of AF4 compounds. Toward this end, it would be of interest to develop an AF4 derivative that itself could undergo a number of different facile reactions. The nature of λ^3-iodanyl compounds and the known 4-iodo AF4 derivative previously synthesized in the Dolbier laboratory[124] was the impetus to synthesize the [(diacetoxy)iodo]-1,1,2,2,9,910,10-octafluoro[2.2]paracyclophane (**4.11**, Scheme 4-4).

The synthesis of iodo-AF4 derivative **4.10** began with nitration of commercially available AF4 by stirring the AF4 with fuming (90%) nitric acid overnight. The nitrated product was then reduced using standard hydrogenation conditions at atmospheric pressure to give the amine in good yield. Sandmeyer conditions were employed to form the diazonium salt intermediate which was oxidized to the iodo-AF4 (**4.11**) by rapidly pouring the dark solution over an excess of potassium iodide. It should be noted that this

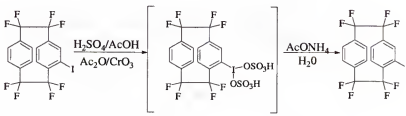
was the most problematic step of the reaction. Following the literature procedure for the diazotization step was not a problem in itself, however, the subsequent oxidation with potassium iodide proved problematic. Treatment of the potassium iodide at 70 °C with the diazonium salt solution resulted in the formation of a disproportionate amount of AF4. A better method for minimizing the formation of the AF4 was to rapidly pour the diazonium salt solution over a large excess (2-3 equivalents) of potassium iodide on ice.



Scheme 4-4: Synthesis of 4-iodo-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane.

A number of reaction conditions were employed with no success in the attempt to form the diacetoxyiodo-AF4 (**4.11**) or the bis(trifluoroacetoxy)iodo-AF4 analogue. Standard conditions were initially used whereby the iodo-AF4 was treated at room temperature with a large excess of peracetic acid formed from equimolar amounts of concentrated sulfuric acid, acetic acid, and hydrogen peroxide at 0 °C. Other reagents described in literature for the oxidation of monovalent iodine such as concentrated nitric acid, Caro's acid, and chromium trioxide[100] were employed with no success. In the reaction of the iodo-AF4 with the latter, the orange color of a solution containing

chromium trioxide, sulfuric acid, acetic acid, and acetic anhydride rapidly changed to a green color upon addition of the iodo-AF4. The color change is completely consistent with a change in the oxidation state from chromium (VI) to chromium (III). An aliquot of the green solution subjected to ^{19}F NMR clearly revealed the formation of a new compound, but upon quenching the solution with excess aqueous ammonium acetate only starting material was obtained. The change in the oxidation state of the chromium and the noticeable formation of an intermediate suggests that the iodo-AF4 is being oxidized to give the intermediate sulfate postulated in equation 4-12.



(4-12)

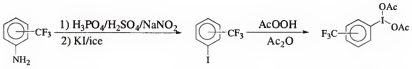
The failure to form the (diacetoxy)iodo-AF4 is difficult to explain. The presence of the perfluorinated ethylene bridges should strongly deactivate the iodo-AF4 as evidenced by the difficulty in oxidizing AF4 to nitro-AF4.[124] The rigidity and steric bulk of the paracyclophane skeleton could prevent the formation of the λ^3-iodane since the acetate ligands occupying the apical positions on the iodane would display a steric interaction regardless of the rotation about the carbon-iodine bond.

4.2.2 Reactivity of Asymmetrical Fluorinated Diaryliodonium Salts

The apparent inability to synthesize the (diacetoxy)iodo-AF4 was prompted us to investigate the formation and reactivity of arene compounds bearing a deactivating substituent. Our model study for this investigation were the isomers of iodo trifluoromethylbenzene since the trifluoromethyl group was expected to mimic the electron withdrawing ability of the perfluorinated ethylene bridges of the AF4. For the

majority of the reactions the *meta*-iodo (trifluoromethyl)benzene was chosen due to the low cost of the starting material and the similarity of the substitution pattern with regard to AF4. Further, it was known from the literature that all three of the (diacetoxyiodo)-trifluoromethylbenzene isomers had been synthesized.[128-130]

The synthesis of *meta*-(diacetoxy)iodobenzene began from the m-(trifluoromethyl)-aniline (**4.12**, Scheme 4-5)which was subjected to Sandmeyer conditions to provide the requisite iodo(trifluoromethyl)benzene (**4.13**). The conversion of **4.13** to the (diacetoxy)-iodobenzene (**4.14**) was easily accomplished by treating a solution of the iodobenzene in 2.5 equivalents of acetic anhydride with an 2.5 equivalents of commercial peracetic acid. The onset of this reaction is marked by a vigorous exotherm and was moderated by using an ice bath although allowing the exothermic reaction to come to reflux did not seem to affect the yield of the product.

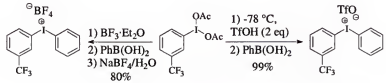


4.12 **4.13 m-CF_3** **4.14 m-CF_3, 67 %**
4.15 p-CF_3, 67%
4.16 o-CF_3, 31 %

Scheme 4-5: The synthesis of m-[(diacetoxy)iodo]trifluoromethylbenzene.

The synthesis of the para- and the ortho- isomers of the iodo(trifluoromethyl)-benzene were synthesized in a similar fashion from the respective commercial iodo(trifluoromethyl)benzene. The yields for the meta- and para- isomers were a modest 67% although the reaction time for the para- isomer was doubled as it was observed that the para- isomer required roughly twice as much time to begin precipitating from solution. Application of the same reaction conditions of the latter to the ortho-substituted isomer gave the ortho-[(diacetoxy)iodo]trifluoromethylbenzene (**4.16**) in only 31% yield.

The syntheses of the o-, m-, and p-isomers of [(diacetoxy)iodotrifluoromethylbenzene provided useful compounds to continue in this vein of chemistry. Further, the difficulty of synthesizing iodo-AF4 with respect to the formation of the trifluoromethylbenzene system suggested that AF4 is unique with respect to the oxidation of the iodine center.



4.18 **4.17**

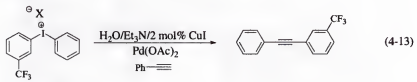
Scheme 4-6. The synthesis of unsymmetrical diaryliodonium salts.

Despite the numerous reactions of diaryliodonium salts reported in the literature, no extensive studies with regard to leaving group ability in nonsymmetrical diaryliodonium compounds have been described in the literature. Oh's research group prepared some unsymmetrical biaryl compounds to investigate the chemoselectivity of reactions of malonate anions with the diaryliodonium salts.[114] They correctly predicted that the more electron-deficient aryl ring coupled preferentially with the malonate.

Toward the formal study of the effect of an electron-withdrawing group in unsymmetrical diaryliodonium salts, in this instance a trifluoromethyl group, we synthesized compounds **4.17** and **4.18** according to Scheme 4-6 following literature procedures.[105,131] The synthesis of each salt was accomplished by using a Lewis acid to activate the iodane toward coupling with the arylboronic ester to give the product in good yield.

To investigate the reactivity of **4.17** and **4.18** and form the foundation for future studies, reactions typical of diaryliodonium salts have been attempted. In particular,

coupling reactions under Sonogashira conditions have been performed. Subjecting a suspension of **4.17** and phenylacetylene to typical Sonogashira coupling conditions resulted in the formation of the phenylacetylene shown in equation 4-13. Unfortunately, the Sonogashira coupling reactions appear to be far from being optimized as the yields from this reaction are horribly low. Similar yields are obtained from the reaction of the sodium tetrafluoroborate salt (**4.18**) with phenylacetylene as well (eq 4-13). Another unidentified byproduct from this reaction was formed in comparable yields to the desired biarylacetylene, **4.19**. ^{19}F NMR of this compound revealed a single resonance near -63 ppm. Further characterization of this crystalline compound by low resolution mass spectroscopy and ^{1}H NMR suggest the formation of another biarylacetylene species containing a trifluoromethyl group.

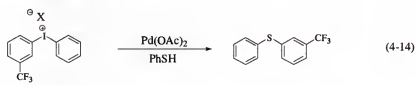


(4-13)

4.17 X=TfO⁻
4.18 X=BF_4^-

4.19

Despite the low yields from and the unknown byproduct that result from the Sonogashira-type coupling reactions, the reaction appears selective for the formation of the product resulting from reaction with the more electron-deficient aryl group. Reaction of **4.17** under palladium catalyzed conditions with thiolphenol to give 1-phenylsulfanyl-3-trifluoromethylbenzene **4.20** (eq 4-14).



(4-14)

4.17 X=TfO⁻

4.20

4.3 Conclusions

The attempted synthesis of hypervalent iodonium compounds of AF4 was not realized using even the strongest oxidizing systems such as Chromium (VI). The lack of reactivity on the part of the iodo-AF4 is assumed to be a combination of steric hindrance encountered between the apical ligands and the highly deactivated electronic nature of the paracyclophane skeleton induced by the perfluoroethylene bridges.

Formation of the isomers of [(diacetoxy)iodo]trifluoromethylbenzene in contrast was facile and provided the intermediate compounds required to form unsymmetrical diaryliodonium salts. Anticipating that the reaction of nucleophiles would react preferentially at the electron-deficient aryl group of the iodonium salt, the reaction of phenylacetylene under Sonogashira conditions provided 1-phenylethynyl-3-trifluoromethylbenzene (**4.19**) as expected providing a basis for future studies.

4.4 Experimental

4-Nitro-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane (4.8): A solution of 8.06 g (22.9 mmol) of 1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane in 60 mL of concentrated nitric acid (fuming, 90%) was stirred overnight at room temperature. The solution was poured into a large beaker containing ice. The precipitate thus formed was flash filtered and washed with water and dried overnight. The crude product was recrystallized from absolute ethanol to give 6.85 g (75%) of the title compound and was identified by fluorine NMR. ^{19}F NMR ($CDCl_3$): δ -113.2 (d, 1F, J=248.2 Hz); -114.48 (d, 1F, J=248.2 Hz); -116.63 (d, 1F, J=391.98, Hz-116.96); (d, 1F, J=219.96 Hz); -117.5 (d, 1F, 236.9 Hz); -117.9 (d, 1F, J=245.3 Hz); -119.1 (d, 1F, J=245.2 Hz); -119.45 (d, 1F, J=245.2 Hz).

4-Amino-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane (4.9): A 250 mL round-bottom flask was charged with 100 mL of anhydrous methanol, 1 equivalent of the nitrated AF4 (**4.8**), 30 equivalents of ammonium formate, and 1 equivalent of 10% palladium on activated carbon. The suspension was cooled to -78 °C and degassed repeatedly under active vacuum. The solution was warmed to room temperature and maintained overnight under a hydrogen atmosphere. The black solution was filtered through a thick pad of silica gel and washed with hot methanol. Concentration of the solution provided a solid which was extracted with ether to remove ammonium formate residue. Removal of the solvent provided the title compound in 93% yield. Purification of the pale yellow solid could be achieved by crystallization from ethanol. ^{19}F NMR ($CDCl_3$): δ -113.2 (d, 1F, J=248.2 Hz); -114.48 (d, 1F, J=248.2 Hz); -116.63 (d, 1F, J=391.98, Hz-116.96); (d, 1F, J=219.96 Hz); -117.5 (d, 1F, 236.9 Hz); -117.9 (d, 1F, J=245.3 Hz); -119.1 (d, 1F, J=245.2 Hz); -119.45 (d, 1F, J=245.2 Hz).

4-Iodo-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane (4.10): A solution of the AF4 amine (**4.9**) (2.0 g, 5.4 mmol) in 8 mL of glacial acetic acid was cooled to 0 °C and 1.5 mL of ice water and 1.5 mL of concentrated sulfuric acid were added in succession. The solution was stirred and sodium nitrate (2.00g, 28.9 mmol) was added. The thick yellow mixture was stirred for 2 hours at 0 °C and rapidly poured over a mixture of potassium iodide (10.4 g, 64.4 mmol) on ice. The dark solution was stirred overnight, filtered, and concentrated to give 4.35 g of crude material. Column chromatography gave 1.35 g (52%) of white solid containing a small amount of inseparable AF4. ^{19}F NMR ($CDCl_3$): δ -109.3 (dd, 1F, J=236.9, 11.8 Hz); -110.5 (dm, 1F, J=242.5 Hz); -113.0 (dm,

1F, J=214.3 Hz); -113.8 (dm, 1F, J=208.7 Hz); -117.1 (d, 1F, 236.9 Hz); -117.5 (d, 1F, J=236.9 Hz); -118.6 (d, 1F, J=236.9 Hz); -119.0 (d, 1F, J=236.9 Hz).

General procedure for the synthesis of o-, m-, and p-[(Diacetoxyiodo)]-trifluoromethylbenzene: A solution of acetic anhydride (2.7 mL, 28.8 mmol, 2.1 equiv), and the iodobenzene (2.0 mL, 13.8 mmol) were introduced into a flask containing a stir bar and fitted with a reflux condenser. Treatment of the solution with peracetic acid (calc'd. as 30% weight solution 4.0 mL, 35.3 mmol, 2.5 equiv) resulted in a spontaneous exothermic reaction which was moderated with an ice bath. The solution was stirred for 7 hours for the *meta-* and *para-* isomers (18 h for *ortho-*) during which time a precipate formed, filtered, and washed with diethyl ether to give varying yields of the diacetates as white solids.

2-(Diacetoxyiodo)trifluoromethylbenzene (4.16): Synthesized following the general procedure in 31% isolated yield. ^{1}H NMR ($CDCl_3$): δ 8.48 (d, 1H, J=7.8 Hz); 7.95 (d, 1H, J=7.5 Hz); 7.79 (t, 1H, J=7.2 Hz); 7.67 (t, 1H, J=7.5 Hz); 1.98 (s, 6H). ^{19}F NMR ($CDCl_3$): δ -65.38 (s, 3F).

3-(Diacetoxyiodo)trifluoromethylbenzene (4.14): Synthesized following the general procedure in 67% isolated yield. ^{1}H NMR ($CDCl_3$): δ 8.1 (d, 1H, J=7.2 Hz); 7.61 (t, 1H, J=7.5 Hz); 7.79 (t, 1H, J=7.2 Hz); 7.5(t, 1H, J=6.6 Hz); 2.0 (s, 6H). ^{19}F NMR ($CDCl_3$): δ -65.38 (s, 3F). HRMS: Calculated for $C_9H_7O_2F_3I$ [M-OAc] (330.944291); found 330.9452.

Phenyl[(3-trifluoromethylphenyl)]iodonium trifluoromethanesulfonate (4.17): A suspension of 3-(diacetoxyiodo)trifluoromethylbenzene (3.6 g, 9.2 mmol) in 40 mL of dichloromethane was cooled to -78 °C and 2 equivalents of trifluoromethanesulfonic acid

(2.65 mL, 18.4 mmol) was added. The solution was kept at -78 °C for 15 minutes, warmed to room temperature, and stirred for 1 hour. The yellow solution was cooled to -78 °C and phenylboronic acid (1.12 g, 9.2 mmol) was added. The solution was brought to room temperature and then gently heated (ca. 35 °C) for 6 hours. Removal of the solvent under reduced pressure left a thick brown sludge which upon treatment with diethyl ether and vigorous stirring gave a white precipitate. The crude product of high purity was collected by suction filtration and washed with diethyl ether and dried under vacuum to give quantitative yield. ^{1}H NMR ($CDCl_3$): δ 8.24 (s, 1H); 8.11 (d, 1H, J=6 Hz); 8.03 (d, 2H, J=7.5 Hz); 7.84 (d, 1H, J=7.8 Hz); 7.67-7.56 (m, 2H); 7.49 (t, 2H, J=8.1 Hz). ^{19}F NMR ($CDCl_3$): δ -63.38 (s, 3F); -78.97 (s, 3F). HRMS (CI): Calculated for $C_{13}H_9F_3I$, 348.970111; found 348.9702 (C13H9F3 I).

Phenyl[(3-trifluoromethylphenyl)]iodonium tetrafluoroborate (4.18): A solution of phenylboronic acid (0.316 g, 2.59 mmol) in 10 mL of dichloromethane was cooled to 0 °C and boron trifluoride etherate (0.32 mL, 2.56 mmol) was added via syringe. The discolored solution was stirred for 15 minutes at 0 °C and a suspension of 3-(diacetoxyiodo) trifluoromethyl benzene in dichloromethane was added to the solution. The solution was stirred for 1 hour at 0 °C and a saturated solution of sodium tetrafluoroborate in 10 mL of water was added. The solution was vigorously stirred for 15 minutes at room temperature and the organic phase extracted with dichloromethane (20 mL). The organic layer was filtered and concentrated, treated with ether to give a finely divided solid and vacuum filtered to give 0.78 g (72%) of crude material as a brown solid. The solid was dissolved in ethanol and ethyl acetate and filtered through a pad of silica. Crystallization gave colorless crystals. ^{1}H NMR ($CDCl_3$): δ 8.75 (s, 1H);

8.54 (d, 1H, J=6.9 Hz); 8.30 (d, 2H, J=8.1 Hz); 8.16 (d, 1H, J=8.1 Hz); 7.8-7.62 (m, 2H); 7.55 (t, 2H, J=7.5 Hz). ^{19}F NMR ($CDCl_3$): δ -61.6 (s, 3F); -148.61 (s, 2.28 F).

(3-trifluoromethylphenyl) phenyl acetylene (4.19): A suspension of the appropriate diaryliodonium salt (1.0 mmol), 1 equivalent of triethylamine, 1 equivalent of potassium carbonate, 2 mol % CuI, and 1 mol % $Pd(OAc)_2$ in 5 mL of water was stirred at room temperature. To this suspension was added 1 equivalent of phenylacetylene. The suspension cleared to give a oily dark residue after stirring for 10 minutes. The solution was stirred for 1 hour and the organics were extracted with diethyl ether, dried with magnesium sulfate, filtered, and concentrated. Column chromatography (hexanes) gave 22.4 mg (9.1%) of **4.19** (R_f=0.34) as a colorless liquid. Alternatively, when $Pd(PPh_3)_2Cl_2$ was employed the yield increased to 31%. ^{1}H NMR ($CDCl_3$): δ 7.81 (s, 1H); 7.7 (d, 1H, J=7.8 Hz); 7.6-7.5 (m, 3H); 7.48 (t, 1H, J=7.5 Hz); 7.43-7.33 (m, 3H). ^{19}F NMR ($CDCl_3$): δ -68.04 (s, 3F). ^{13}C NMR ($CDCl_3$): δ 130.12, 127.2, 126.66, 126.22, 124.37, 124.25, 123.9, 123.87 (q, J=4.35 Hz), 121.03, 120.25 (q, J=3.75 Hz), 119.72, 118.06, 117.42, 86.37, 83.27.

3-(trifluoromethyl)phenyl thiophenol (4.20): A suspension of 0.3 g of the diaryliodonium salt (**4.17**), 5 mol% palladium (II) acetate (0.007 g), 2 equivalents of potassium carbonate in anhydrous THF was stirred at room temperature. Addition of 1 equivalent of thiobenzene gave a yellow solution which was allowed to stir overnight. The solution was taken up in 10 mL of ethyl ether and washed with 3-5 mL portions of water. The ether layer was dried with magnesium sulfate, filtered, and concentrated to provide the product as a yellow oil in 43% yield. ^{1}H NMR ($CDCl_3$): δ 7.7 (d, 1H); 7.45

(d, 1H); 7.4-7.1 (m, 5H); 7.1 (t, 3H). ^{19}F NMR ($CDCl_3$): δ -63.3 (s, 3F). HRMS (EI): Calculated for $C_{13}H_9SF_3$ 254.037706; found 254.0370.

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BIOGRAPHICAL SKETCH

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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